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Lamotrigine 25mg, 50mg, 100mg and 200mg Tablets

PL 36390/0030-3

LAY SUMMARY

On 18th April 2012, the MHRA granted Marketing Authorisations (licences) for the medicinal products Lamotrigine 25, 50, 100 and 200 mg Tablets (PL 36390/0030-3). These medicines are only available on prescription from your doctor.

The active ingredient in this product is lamotrigine, which belongs to a group of medicines called anti-epileptics. It is used to treat two conditions – epilepsy and bipolar disorder (sometimes called manic depression). It treats epilepsy by blocking the signals in the brain that trigger epileptic seizure (fits). It is not known how lamotrigine works in the brain to have this effect.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lamotrigine 25, 50, 100 and 200mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Lamotrigine 25mg, 50mg, 100mg and 200mg Tablets

PL 36390/0030-3

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare Products Regulatory Agency (MHRA) granted marketing authorisations (licences) for the medicinal products Lamotrigine 25, 50, 100 and 200mg Tablets (PL 36390/0030-3) to STD Chemicals Limited on the 18th April 2012.

These prescription only medicines (POM) are used for the following conditions.

Epilepsy
*Adults and adolescents aged 13 years and above*
- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

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

*Children and adolescents aged 2 to 12 years*
- Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

- Monotherapy of typical absence seizures.

Bipolar disorder
*Adults aged 18 years and above*
- Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes.

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

These applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC as amended, cross-referring to Lamotrigine 25, 50, 100 and 200mg Tablets, first approved to Neolab Ltd on 12th May 2005 (PL 08137/0108-10). These licenses underwent a change of ownership to Fannin (UK) Limited on 26th August 2011 (PL 20417/0050-3).

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated.

A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.

No environmental risk assessment (ERA) has been undertaken, as this is not considered necessary. This product is essentially similar and the therapeutic indications and posology of the finished products are the same as those already licensed products. The applicant’s justification for absence of ERA is satisfactory.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0030-3
PROPRIETARY NAME: Lamotrigine 25, 50, 100 and 200mg Tablets
COMPANY NAME: STD Chemicals Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1 INTRODUCTION
These are informed consent applications for Lamotrigine 25, 50, 100 and 200mg Tablets, submitted under Article 10c of Directive 2001/83/EC as amended. These products are cross-referring to Lamotrigine 25, 50, 100 and 200mg Tablets, first approved to Neolab Ltd on 12th May 2005 (PL 08137/0108-10). The licenses (PL 08137/0108-10) underwent a change of ownership to Fannin (UK) Limited on 26th August 2011 (PL 20417/0050-3). The current applications are considered valid.

2 MARKETING AUTHORISATION APPLICATION (MAA)

2.1 Name(s)
The proposed names of the products are Lamotrigine 25, 50, 100 and 200mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product is a tablet for oral use and contains 25mg, 50mg 100mg or 200mg of the active ingredient lamotrigine.

The tablets are packed in blister strips comprising polyvinylchloride/Aluminium foil enclosed in an outer carton with pack sizes of 21, 28, 42, 56 or 100 tablets (not all packs may be marketed).

The packaging and pack sizes are the same as those for the cross-reference products.

The proposed shelf life is 36 months with a storage condition “Store in the original package”. The shelf-life and storage condition are identical to those for the cross-reference products and are satisfactory.

2.3 Legal status
These products are Prescription Only Medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum full scale batch size is stated.

2.8 Finished product specifications
The proposed finished product specifications, at release and shelf-life, are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification conforms to the current European Pharmacopoeia monograph for lamotrigine and is in-line with those for the cross-reference products.

2.10 TSE Compliance
No materials of human or animal origin have been used in the manufacture of these products. This is consistent with the reference products.

Confirmation has been provided that the magnesium stearate used in the tablet is of vegetable origin. The milk used in the product of the lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the cross-reference products Lamotrigine 25, 50, 100 and 200mg Tablets (PL 20417/0050-3).

3 EXPERT REPORTS
The applicant has included detailed expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4 PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products are identical to those of the cross-reference products.

5 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6 PATIENT INFORMATION LEAFLET (PIL)/LABELLING
A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-
structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the applications are acceptable. The grant of marketing authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and, as such, have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications for Lamotrigine 25, 50, 100 and 200mg Tablets, first approved to Neolab Ltd on 12th May 2005 (PL 08137/0108-10). These licenses underwent a change of ownership to Fannin (UK) Limited on 26th August 2011 (PL 20417/0050-3).

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with lamotrigine is considered to have demonstrated the therapeutic values of the compounds. The risk benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 7(^{th}) March 2011</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications are valid on 16(^{th}) March 2011</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 14(^{th}) June 2011 and 15(^{th}) February 2012</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 11(^{th}) October 2011 and 20(^{th}) February 2012</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 18(^{th}) April 2012</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains lamotrigine 25 mg.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
Lamotrigine 25 mg Tablets are yellow, round tablets with “25” on one side and scored on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy

_Adults and adolescents aged 13 years and above_
Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

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

_Children and adolescents aged 2 to 12 years_
Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Monotherapy of typical absence seizures.

Bipolar disorder

_Adults aged 18 years and above_
Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

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

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

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

Restarting Therapy
Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued lamotrigine 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.
It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

Epilepsy

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td></td>
</tr>
</tbody>
</table>
| To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved.
500 mg/day has been required by some patients to achieve desired response. |
| **Adjunctive therapy WITH valproate** (inhibitor of lamotrigine glucuronidation – see section 4.5): | | | |
| This dosage regimen should be used with valproate regardless of any concomitant medicinal products | 12.5 mg/day (given as 25 mg on alternate days) | 25 mg/day (once a day) | 100 – 200 mg/day (once a day or two divided doses) |
| To achieve maintenance, doses may be increased by maximum of 50 – 50 mg every one to two weeks until optimal response is achieved. |
| **Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation** (see section 4.5): | | | |
| This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir | 50 mg/day (once a day) | 100 mg/day (two divided doses) | 200 – 400 mg/day (two divided doses) |
| To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved.
700 mg/day has been required by some patients to achieve desired response. |
| **Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation** (see section 4.5): | | | |
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy of typical absence seizures:</strong></td>
<td>0.3 mg/kg/day (once a day or two divided doses)</td>
<td>0.6 mg/kg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):</strong></td>
<td>0.15 mg/kg/day* (once a day)</td>
<td>0.3 mg/kg/day (once a day)</td>
<td>1 – 5 mg/kg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):</strong></td>
<td>0.6 mg/kg/day (two divided doses)</td>
<td>1.2 mg/kg/day (two divided doses)</td>
<td>5 – 15 mg/kg/day (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

Table 2: Children and adolescents aged 2 to 12 years - recommended treatment regimen in epilepsy (total daily dose in mg/kg body weight/day)
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Doses in the range 100 - 400 mg/day used in clinical trials.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Adju
This dosage regimen should be used with valproate regardless of any concomitant medicinal products

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg/day</td>
<td>(given as 25 mg on alternate days)</td>
</tr>
<tr>
<td>25 mg/day</td>
<td>(once a day)</td>
</tr>
<tr>
<td>50 mg/day</td>
<td>(once a day or two divided doses)</td>
</tr>
<tr>
<td>100 mg/day</td>
<td>- usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td>Maximum dose of 200 mg/day can be used depending on clinical response.</td>
</tr>
</tbody>
</table>

**Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation** (see section 4.5):

This dosage regimen should be used without valproate but with:
- phenytoin
- carbamazepine
- phenobarbitone
- primidone
- rifampicin
- lopinavir/ritonavir.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/day</td>
<td>(once a day)</td>
</tr>
<tr>
<td>100 mg/day</td>
<td>(two divided doses)</td>
</tr>
<tr>
<td>200 mg/day</td>
<td>(two divided doses)</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)</td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

* The Target stabilisation dose will alter depending on clinical response

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to withdrawal)</th>
<th>Week 1 (beginning with withdrawal)</th>
<th>Week 2</th>
<th>Week 3 onwards *</th>
</tr>
</thead>
</table>

**Withdrawal of valproate** (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:

When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/day</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Maintain this dose (200 mg/day) (two divided doses)</td>
<td></td>
</tr>
<tr>
<td>200 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>400 mg/day</td>
<td>Maintain this dose (400 mg/day)</td>
</tr>
</tbody>
</table>

**Withdrawal of inducers of lamotrigine glucuronidation** (see section 4.5), depending on original dose of lamotrigine:

This dosage regimen should be used when the following are withdrawn:

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>225 mg/day</td>
</tr>
<tr>
<td>150 mg/day</td>
<td></td>
</tr>
</tbody>
</table>
phenytoin  
carbamazepine  
phenobarbitone  
primidone  
rifampicin  
lopinavir/ritonavir

<table>
<thead>
<tr>
<th></th>
<th>200 mg/day</th>
<th>200 mg/day</th>
<th>150 mg/day</th>
<th>100 mg/day</th>
</tr>
</thead>
</table>

**Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation** (see section 4.5):

This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn.

Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 - 400 mg/day)

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.

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

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to addition)</th>
<th>Week 1 (beginning with addition)</th>
<th>Week 2</th>
<th>Week 3 onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addition of valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products</td>
<td>200 mg/day</td>
<td>100 mg/day</td>
<td>Maintain this dose (100 mg/day)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg/day</td>
<td>150 mg/day</td>
<td>Maintain this dose (150 mg/day)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day)</td>
<td></td>
</tr>
<tr>
<td><strong>Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate</strong> (see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when the following are added without valproate: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir.</td>
<td>200 mg/day</td>
<td>200 mg/day</td>
<td>300 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td></td>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>225 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td></td>
<td>100 mg/day</td>
<td>100 mg/day</td>
<td>150 mg/day</td>
<td>200 mg/day</td>
</tr>
</tbody>
</table>
Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):

This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added.

Maintain target dose achieved in dose escalation (200 mg/day; dose range 100-400 mg/day)

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.

**Discontinuation of Lamotrigine in patients with bipolar disorder**

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

**Children and adolescents below 18 years**

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

**General dosing recommendations for lamotrigine in special patient population**

**Women taking hormonal contraceptives**

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

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

The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

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

The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of
lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

Starting lamotrigine in patients already taking hormonal contraceptives
Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation
Adjustment to the recommended maintenance dose of lamotrigine may not be required.

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Elderly (above 65 years)
No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population (see section 5.2).

Renal impairment
Caution should be exercised when administering 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).

Hepatic impairment
Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Lamotrigine Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.4 Special warnings and precautions for use
Skin rash
There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life threatening skin rashes including Stevens Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

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

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

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

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

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

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

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 (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including lamotrigine. Therefore patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Hormonal contraceptives

*Effects of hormonal contraceptives on lamotrigine efficacy*

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

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

*Effects of lamotrigine on hormonal contraceptive efficacy*

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine has a slight inhibitory effect on dihydrofolate acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.
Renal failure
In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

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

Development in children
There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.

Precautions relating to epilepsy
As with other AEDs, abrupt withdrawal of 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 two weeks.

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

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

Myoclonic seizures may be worsened by lamotrigine.

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

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

Precautions relating to bipolar disorder

Children and adolescents below 18 years
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

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

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.
Table 6: Effects of other medicinal products on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Medicinal products that significantly inhibit glucuronidation of lamotrigine</th>
<th>Medicinal products that significantly induce glucuronidation of lamotrigine</th>
<th>Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Phenobarbitone</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Primidone</td>
<td>Rifampicin</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Ethinylestradiol/levonorgestrel combination**</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Atazanavir/ritonavir*</td>
<td></td>
<td>Lithium</td>
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<tr>
<td></td>
<td></td>
<td>Buproprion</td>
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<td></td>
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<td>Olanzapine</td>
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<tr>
<td></td>
<td></td>
<td>Aripiprazole</td>
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</tbody>
</table>

*For dosing guidance (see section 4.2)

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

Interactions involving antiepileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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

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

Based on a retrospective analysis of plasma levels in patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.
Potential interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

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

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

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

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

**Interactions involving other psychoactive agents**

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

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

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

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

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

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

**Interactions involving hormonal contraceptives**

**Effect of hormonal contraceptives on lamotrigine pharmacokinetics**

In a study of 16 female volunteers, dosing with 30 μg ethinylestradiol/150 μg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in
lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics
In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products
In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

Data from in vitro assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is a more potent in vitro inhibitor of OCT 2 than cimetidine, with IC50 values of 53.8 µM and 186 µM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

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

4.6 Fertility, Pregnancy and lactation
Risk related to antiepileptic drugs in general.

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

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

Risk related to lamotrigine.

**Pregnancy**

Postmarketing data from several prospective pregnancy registers have documented outcomes in over 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall these data do not suggest a substantial increase in the risk for congenital malformations, although data are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).

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

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels (see section 4.4). Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

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

**Lactation**

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother’s. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. Among a limited group of exposed infants, no adverse effects were observed.

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

**Fertility**

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

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

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

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

### 4.8 Undesirable effects

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine.
The following convention has been utilised for the classification of undesirable effects:

Very common (≥1/10),
Common (≥1/100, <1/10),
Uncommon (≥1/1000, <1/100),
Rare (≥1/10,000, <1/1000),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Epilepsy

Blood and lymphatic system disorders
Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis.

Frequency not known: lymphadenopathy

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

Immune system disorders
Very rare: hypersensitivity syndrome** (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi-organ failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Psychiatric disorders
Common: aggression, irritability.
Very rare: confusion, hallucinations, tics.

Nervous system disorders
During monotherapy clinical trials:
Very common: headache.
Common: somnolence, dizziness, tremor, insomnia.
Uncommon: ataxia.
Rare: nystagmus.

During other clinical experience:
Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

Frequency not known: aseptic meningitis

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.
**Eye disorders**
During monotherapy clinical trials:
Uncommon: diplopia, blurred vision.

During other clinical experience:
Rare: conjunctivitis.

**Gastrointestinal disorders**
During monotherapy clinical trials:
Common: nausea, vomiting, diarrhoea.

**Hepato-biliary disorders**
Very rare: hepatic failure, hepatic dysfunction, increased liver function tests.

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

**Skin and subcutaneous tissue disorders**
Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

In double-blind, adjunctive clinical trials in adults, 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).

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

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

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

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

**Musculoskeletal and connective tissue disorders**
Very rare: lupus-like reactions.

**General disorders and administration site conditions**
Common: tiredness.

**Bipolar Disorder**

The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

**Nervous system disorders**
During bipolar disorder clinical trials:

Very common: headache.
Common: agitation, somnolence, dizziness.

**Gastrointestinal disorders**
During bipolar disorder clinical trials:
Common: dry mouth

Skin and subcutaneous tissue disorders
During bipolar disorder clinical trials:

Very common: skin rash.
Rare: Stevens–Johnson Syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Musculoskeletal and connective tissue disorders
During bipolar disorder clinical trials:

Common: arthralgia.

General disorders and administration site conditions
During bipolar disorder clinical trials:
Common: pain, back pain.

4.9 **Overdose**

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

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

5 **PHARMACOLOGICAL PROPERTIES**

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antiepileptics, ATC Code: N03 A X09

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

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

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

In another study, single oral doses of 600mg 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 150mg and 300mg did not differ from placebo.

Clinical efficacy and safety in children aged 1 to 24 months
The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase (for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, CI 95% -2.6% < > 50.2%, p=0.07.

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

Clinical efficacy and safety in Lennox-Gastaut syndrome
There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

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

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

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

<table>
<thead>
<tr>
<th>‘Proportion’ of patients being event free at week 76</th>
<th>Study SCAB2003</th>
<th>Study SCAB2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criterion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive episode</td>
<td>Lamotrigine</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Major manic episode</td>
<td>Lamotrigine</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>0.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Intervention free</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.023</td>
<td>0.006</td>
</tr>
</tbody>
</table>
In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine-treated patients had significantly longer times to first depressive episode than placebo patients, and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant. The efficacy of lamotrigine in combination with mood stabilisers has not been adequately studied.

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

5.2 Pharmacokinetic properties

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

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

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

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

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P<sub>450</sub> enzymes are unlikely to occur.

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

The half-life of lamotrigine is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see section 4.2).
Linearity
The pharmacokinetics of lamotrigine are linear up to 450 mg, the highest single dose tested.

Special patient populations

Children
Clearance adjusted for bodyweight is higher in children aged 12 years and under 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 drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see 4.2 Posology and method of administration).

Infants aged 2 to 26 months
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher Cmax levels are likely to be observed in some children with a body weight below 10 kg.

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

Renal impairment
Twelve volunteers with chronic renal failure and another six individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient’s concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

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

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but reduced foetal weight and retarded skeletal ossification were observed, at exposure levels below or similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to severity of maternal toxicity, the teratogenic potential of lamotrigine has not been characterised above clinical exposure.

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

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

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

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC50 was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section 5.1).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycollate

Iron oxide yellow (E172)

Maize starch

Magnesium stearate

6.2 Incompatibilities
None reported.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister strips comprising PVC/Aluminium foil enclosed in an outer carton. Pack sizes of 21, 28, 42, 56 or 100 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/04/2012

10 DATE OF REVISION OF THE TEXT
18/04/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 50 mg Tablets.

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Lamotrigine 50 mg Tablets are yellow, round tablets with “50” on one side and scored on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Epilepsy

Adults and adolescents aged 13 years and above
Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

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

Children and adolescents aged 2 to 12 years
Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Monotherapy of typical absence seizures.

Bipolar disorder

Adults aged 18 years and above
Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

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

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

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

Restarting Therapy
Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued lamotrigine 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.
It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

**Epilepsy**

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/day (once a day)</td>
<td>25 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td></td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved.

500 mg/day has been required by some patients to achieve desired response.

*Adjunctive therapy WITH valproate* (inhibitor of lamotrigine glucuronidation – see section 4.5):

| This dosage regimen should be used with valproate regardless of any concomitant medicinal products | 12.5 mg/day (given as 25 mg on alternate days) | 25 mg/day (once a day) | 100 – 200 mg/day (once a day or two divided doses) |

To achieve maintenance, doses may be increased by maximum of 25 - 50 mg every one to two weeks until optimal response is achieved.

*Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation* (see section 4.5):

| This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir | 50 mg/day (once a day) | 100 mg/day (two divided doses) | 200 – 400 mg/day (two divided doses) |

To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved.

700 mg/day has been required by some patients to achieve desired response.

*Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation* (see section 4.5):
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>25 mg/day (once a day)</th>
<th>50 mg/day (once a day)</th>
<th>100 – 200 mg/day (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25 mg/day</strong></td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>50 mg/day</strong></td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>100 mg/day</strong></td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>200 mg/day</strong></td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved.

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy of typical absence seizures:</td>
<td>0.3 mg/kg/day (once a day or two divided doses)</td>
<td>0.6 mg/kg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses)</td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):</th>
<th>0.15 mg/kg/day* (once a day)</th>
<th>0.3 mg/kg/day (once a day)</th>
<th>1 – 5 mg/kg/day (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):</th>
<th>0.6mg/kg/day (two divided doses)</th>
<th>1.2 mg/kg/day (two divided doses)</th>
<th>5 – 15 mg/kg/day (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):</th>
<th>0.6mg/kg/day (two divided doses)</th>
<th>1.2 mg/kg/day (two divided doses)</th>
<th>5 – 15 mg/kg/day (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

### Children below 2 years
There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus lamotrigine is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2.

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This dosage regimen should be used with valproate regardless of any concomitant medicinal products.

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>12.5 mg/day (given as 25 mg on alternate days)</th>
<th>25 mg/day (once a day)</th>
<th>50 mg/day (once a day or two divided doses)</th>
<th>100 mg/day - usual target dose for optimal response (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum dose of 200 mg/day can be used depending on clinical response.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):

This dosage regimen should be used without valproate but with:
- phenytoin
- carbamazepine
- phenobarbitone
- primidone
- rifampicin
- lopinavir/ritonavir.

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>50 mg/day (once a day)</th>
<th>100 mg/day (two divided doses)</th>
<th>200 mg/day (two divided doses)</th>
<th>300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

* The Target stabilisation dose will alter depending on clinical response

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to withdrawal)</th>
<th>Week 1 (beginning with withdrawal)</th>
<th>Week 2</th>
<th>Week 3 onwards *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week</td>
<td>100 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day) (two divided doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg/day</td>
<td>300 mg/day</td>
<td>400 mg/day</td>
<td>Maintain this dose (400 mg/day)</td>
</tr>
</tbody>
</table>

Withdrawal of inducers of lamotrigine glucuronidation (see section 4.5), depending on original dose of lamotrigine:
This dosage regimen should be used when the following are withdrawn: phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>400 mg/day</th>
<th>400 mg/day</th>
<th>300 mg/day</th>
<th>200 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg/day</td>
<td>400 mg/day</td>
<td>300 mg/day</td>
<td>225 mg/day</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>300 mg/day</td>
<td>200 mg/day</td>
<td>150 mg/day</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>200 mg/day</td>
<td>200 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):

<table>
<thead>
<tr>
<th>Dosage</th>
<th>400 mg/day</th>
<th>400 mg/day</th>
<th>300 mg/day</th>
<th>200 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg/day</td>
<td>400 mg/day</td>
<td>300 mg/day</td>
<td>225 mg/day</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>300 mg/day</td>
<td>300 mg/day</td>
<td>200 mg/day</td>
<td>150 mg/day</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>200 mg/day</td>
<td>200 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.

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

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to addition)</th>
<th>Week 1 (beginning with addition)</th>
<th>Week 2</th>
<th>Week 3 onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products</td>
<td>200 mg/day</td>
<td>100 mg/day</td>
<td>Maintain this dose (100 mg/day)</td>
<td></td>
</tr>
<tr>
<td>300 mg/day</td>
<td>150 mg/day</td>
<td>Maintain this dose (150 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate (see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when the following are added without valproate: phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir.</td>
<td>200 mg/day</td>
<td>200 mg/day</td>
<td>300 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>225 mg/day</td>
<td>300 mg/day</td>
<td></td>
</tr>
<tr>
<td>100 mg/day</td>
<td>100 mg/day</td>
<td>150 mg/day</td>
<td>200 mg/day</td>
<td></td>
</tr>
</tbody>
</table>
Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):

| This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added | Maintain target dose achieved in dose escalation (200 mg/day; dose range 100–400 mg/day) |

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.

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

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

General dosing recommendations for lamotrigine in special patient populations

Women taking hormonal contraceptives
The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation
The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation
The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive
that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

Starting lamotrigine in patients already taking hormonal contraceptives
Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation
Adjustment to the recommended maintenance dose of lamotrigine may not be required.

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Elderly (above 65 years)
No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population (see section 5.2).

Renal impairment
Caution should be exercised when administering 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).

Hepatic impairment
Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

4.4 Special warnings and precautions for use
Skin rash
There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life threatening skin rashes including Stevens Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

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

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

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

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

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

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

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 (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

**Clinical worsening and suicide risk**

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including lamotrigine. Therefore patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

**Hormonal contraceptives**

*Effects of hormonal contraceptives on lamotrigine efficacy*

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

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

*Effects of lamotrigine on hormonal contraceptive efficacy*

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

**Dihydrofolate reductase**

Lamotrigine has a slight inhibitory effect on dihydrofolate reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.
Renal failure
In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

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

Development in children
There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.

Precautions relating to epilepsy
As with other AEDs, abrupt withdrawal of 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 two weeks.

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

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

Myoclonic seizures may be worsened by lamotrigine.

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

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

Precautions relating to bipolar disorder

*Children and adolescents below 18 years*
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

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

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

*Table 6: Effects of other medicinal products on glucuronidation of lamotrigine*

<table>
<thead>
<tr>
<th>Medicinal products that significantly inhibit glucuronidation of lamotrigine</th>
<th>Medicinal products that significantly induce glucuronidation of lamotrigine</th>
<th>Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Oxcarbazepine</td>
</tr>
</tbody>
</table>
Interactions involving antiepileptic drugs

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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

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

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

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

Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg, 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.
Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

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

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

**Interactions involving other psychoactive agents**

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

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

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

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

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

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

**Interactions involving hormonal contraceptives**

**Effect of hormonal contraceptives on lamotrigine pharmacokinetics**

In a study of 16 female volunteers, dosing with 30 μg ethinylloestradiol/150 μg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).
**Effect of lamotrigine on hormonal contraceptive pharmacokinetics**

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

**Interactions involving other medicinal products**

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

Data from *in vitro* assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is a more potent *in vitro* inhibitor of OCT 2 than cimetidine, with IC50 values of 53.8 µM and 186 µM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

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

4.6 **Fertility, Pregnancy and lactation**

**Risk related to antiepileptic drugs in general.**

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

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

Pregnancy

Postmarketing data from several prospective pregnancy registers have documented outcomes in over 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall these data do not suggest a substantial increase in the risk for congenital malformations, although data are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).

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

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofetal damage by reducing folic acid levels (see section 4.4). Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

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

Lactation

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother’s. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. Among a limited group of exposed infants, no adverse effects were observed.

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine.

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

Very common (≥1/10),
Common (≥1/100, <1/10),
Uncommon (≥1/1000, <1/100),
Rare (≥1/10,000, <1/1000),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Epilepsy**

**Blood and lymphatic system disorders**

Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis.

Frequency not known: lymphadenopathy

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

**Immune system disorders**

Very rare: hypersensitivity syndrome** (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi-organ failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

**Psychiatric disorders**

Common: aggression, irritability.

Very rare: confusion, hallucinations, tics.

**Nervous system disorders**

During monotherapy clinical trials:

Very common: headache.

Common: somnolence, dizziness, tremor, insomnia.

Uncommon: ataxia.

Rare: nystagmus.

During other clinical experience:

Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

Frequency not known: aseptic meningitis

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.

**Eye disorders**

During monotherapy clinical trials:

Uncommon: diplopia, blurred vision.
During other clinical experience:
Rare: conjunctivitis.

Gastrointestinal disorders
During monotherapy clinical trials:
Common: nausea, vomiting, diarrhoea.

Hepato-biliary disorders
Very rare: hepatic failure, hepatic dysfunction, increased liver function tests.

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

Skin and subcutaneous tissue disorders
Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

In double-blind, adjunctive clinical trials in adults, 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).

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

The overall risk of rash appears to be strongly associated with:
- high initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

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

Musculoskeletal and connective tissue disorders
Very rare: lupus-like reactions.

General disorders and administration site conditions
Common: tiredness.

Bipolar Disorder
The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

Nervous system disorders
During bipolar disorder clinical trials:
Very common: headache.
Common: agitation, somnolence, dizziness.

Gastrointestinal disorders
During bipolar disorder clinical trials:
Common: dry mouth
**Skin and subcutaneous tissue disorders**
During bipolar disorder clinical trials:

Very common: skin rash.
Rare: Stevens-Johnson Syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

**Musculoskeletal and connective tissue disorders**
During bipolar disorder clinical trials:

Common: arthralgia.

**General disorders and administration site conditions**
During bipolar disorder clinical trials:

Common: pain, back pain.

### 4.9 Overdose

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

**Treatment**
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** other antiepileptics, ATC Code: N03 A X09

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

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

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

In another study, single oral doses of 600mg 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 150mg and 300mg did not differ from placebo.
Clinical efficacy and safety in children aged 1 to 24 months
The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase (for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, CI95% -2.6% < > 50.2%, p=0.07.

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

Clinical efficacy and safety in Lennox-Gastaut syndrome
There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

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

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

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

<table>
<thead>
<tr>
<th>‘Proportion’ of patients being event free at week 76</th>
<th>Study SCAB2003</th>
<th>Study SCAB2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criterion</strong></td>
<td>Bipolar 1</td>
<td>Bipolar 1</td>
</tr>
<tr>
<td><strong>Major depressive episode</strong></td>
<td>Lamotrigine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Intervention free</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>Depression free</td>
<td>0.51</td>
<td>0.46</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.047</td>
<td>0.209</td>
</tr>
<tr>
<td>Free of mania</td>
<td>0.70</td>
<td>0.86</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.339</td>
<td>0.026</td>
</tr>
</tbody>
</table>

A total of 256 subjects between 1 to 24 months of age have been exposed to lamotrigine in the dose range 1 to 15 mg/kg/day for up to 72 weeks. The safety profile of lamotrigine in children aged 1 month to 2 years was similar to that in older children except that clinically significant worsening of seizures (>=50%) was reported more often in children under 2 years of age (26%) as compared to older children (14%).
In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine-treated patients had significantly longer times to first depressive episode than placebo patients, and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

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

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

5.2 Pharmacokinetic properties

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

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

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

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

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

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

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

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

Special patient populations

Children
Clearance adjusted for bodyweight is higher in children aged 12 years and under 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 drugs such as carbamazepine and phenytoin and increasing to mean values
of 45 to 50 hours when co-administered with sodium valproate alone (see 4.2 Posology and method of administration).

**Infants aged 2 to 26 months**
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher Cmax levels are likely to be observed in some children with a body weight below 10 kg.

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

**Renal impairment**
Twelve volunteers with chronic renal failure and another six individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient’s concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

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

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

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

In rats, enhanced foetal as well as postnatal mortality was observed when lamotrigine was administered during late gestation and through the early post-natal period. These effects were observed at the expected clinical exposure.
In juvenile rats, an effect on learning in the Biel maze test, a slight delay in balanopreputial separation and vaginal patency and a decreased postnatal body weight gain in F1 animals were observed at exposures approximately two-times higher than the therapeutic exposures in human adults.

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

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC50 was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section 5.1).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycollate
Iron oxide yellow (E172)
Maize starch
Magnesium stearate

6.2 Incompatibilities
None reported.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in the original package

6.5 Nature and contents of container
Blisters strips comprising PVC/Aluminium foil enclosed in an outer carton. Pack sizes of 21, 28, 42, 56 or 100 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/04/2012
DATE OF REVISION OF THE TEXT
18/04/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 100 mg Tablets.

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Lamotrigine 100 mg Tablets are yellow, round tablets with “100” on one side and scored on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Epilepsy

Adults and adolescents aged 13 years and above
Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

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

Children and adolescents aged 2 to 12 years
Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Monotherapy of typical absence seizures.

Bipolar disorder

Adults aged 18 years and above
Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

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

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

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

Restarting Therapy
Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued lamotrigine 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.
It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

Epilepsy

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/day (once a day)</td>
<td>50 mg/day</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with valproate regardless of any concomitant medicinal products</td>
<td>12.5 mg/day (given as 25 mg on alternate days)</td>
<td>25 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 25 - 50 mg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700 mg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ ritonavir</td>
<td>50 mg/day (once a day)</td>
<td>100 mg/day (two divided doses)</td>
<td>200 – 400 mg/day (two divided doses)</td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700 mg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Children and adolescents aged 2 to 12 years – recommended treatment regimen in epilepsy**

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg/kg/day (once a day)</td>
<td>10 mg/kg/day</td>
<td>30 – 60 mg/kg/day (once a day)</td>
<td></td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 10 mg/kg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg/kg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with valproate regardless of any concomitant medicinal products</td>
<td>1.25 mg/kg/day (given as 2.5 mg/kg on alternate days)</td>
<td>5 mg/kg/day (once a day)</td>
<td>15 – 30 mg/kg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 5 mg/kg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg/kg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ ritonavir</td>
<td>5 mg/kg/day (once a day)</td>
<td>10 mg/kg/day (two divided doses)</td>
<td>15 – 30 mg/kg/day (two divided doses)</td>
</tr>
<tr>
<td>To achieve maintenance, doses may be increased by maximum of 10 mg/kg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg/kg/day has been required by some patients to achieve desired response.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day (once a day)</td>
<td>0.3 mg/kg/day (once a day or two divided doses)</td>
<td>0.6 mg/kg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses)</td>
</tr>
<tr>
<td>50 mg/day (once a day)</td>
<td>0.6 mg/kg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved.

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy of typical absence seizures:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 mg/kg/day (once a day)</td>
<td>0.3 mg/kg/day (once a day)</td>
<td>1 – 5 mg/kg/day (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.</td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 mg/kg/day (two divided doses)</td>
<td>1.2 mg/kg/day (two divided doses)</td>
<td>5 – 15 mg/kg/day (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 mg/kg/day (two divided doses)</td>
<td>1.2 mg/kg/day (two divided doses)</td>
<td>5 – 15 mg/kg/day (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

This dosage regimen should be used without valproate but with:

- phenytoin
- carbamazepine
- phenobarbitone
- primidone
- rifampicin
- lopinavir/ritonavir.
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Doses in the range 100 - 400 mg/day used in clinical trials.</td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg every one to two weeks until optimal response is achieved, with a maximum of maintenance dose of 200 mg/day.

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

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

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

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

Children below 2 years

There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus lamotrigine is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2.

Bipolar disorder

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Doses in the range 100 - 400 mg/day used in clinical trials.</td>
</tr>
</tbody>
</table>

**Adjunctive therapy WITH valproate** (inhibitor of lamotrigine glucuronidation – see section 4.5):
This dosage regimen should be used with valproate regardless of any concomitant medicinal products:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>12.5 mg/day (given as 25 mg on alternate days)</th>
<th>25 mg/day (once a day)</th>
<th>50 mg/day (once a day or two divided doses)</th>
<th>100 mg/day - usual target dose for optimal response (once a day or two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum dose of 200 mg/day can be used depending on clinical response.</td>
<td></td>
</tr>
</tbody>
</table>

Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):

This dosage regimen should be used without valproate but with:
- phenytoin
- carbamazepine
- phenobarbitone
- primidone
- rifampicin
- lopinavir/ritonavir.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>50 mg/day (once a day)</th>
<th>100 mg/day (two divided doses)</th>
<th>200 mg/day (two divided doses)</th>
<th>300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

* The Target stabilisation dose will alter depending on clinical response

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to withdrawal)</th>
<th>Week 1 (beginning with withdrawal)</th>
<th>Week 2</th>
<th>Week 3 onwards *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week</td>
<td>100 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day) (two divided doses)</td>
<td>Maintain this dose (400 mg/day)</td>
</tr>
<tr>
<td></td>
<td>200 mg/day</td>
<td>300 mg/day</td>
<td>400 mg/day</td>
<td></td>
</tr>
<tr>
<td>Withdrawal of inducers of lamotrigine glucuronidation (see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when the following are withdrawn:</td>
<td>400 mg/day</td>
<td>400 mg/day</td>
<td>300 mg/day</td>
<td>200 mg/day</td>
</tr>
<tr>
<td></td>
<td>300 mg/day</td>
<td>300 mg/day</td>
<td>225 mg/day</td>
<td>150 mg/day</td>
</tr>
</tbody>
</table>
phenytoin  
carbamazepine  
phenobarbitone  
primidone  
rifampicin  
lopinavir/ritonavir

<table>
<thead>
<tr>
<th></th>
<th>200 mg/day</th>
<th>200 mg/day</th>
<th>150 mg/day</th>
<th>100 mg/day</th>
</tr>
</thead>
</table>

**Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):**

This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn.

Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 - 400 mg/day)

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.

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

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to addition)</th>
<th>Week 1 (beginning with addition)</th>
<th>Week 2</th>
<th>Week 3 onwards</th>
</tr>
</thead>
</table>

**Addition of valproate** (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:

This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products

<table>
<thead>
<tr>
<th></th>
<th>200 mg/day</th>
<th>100 mg/day</th>
<th>Maintain this dose (100 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg/day</td>
<td>150 mg/day</td>
<td>Maintain this dose (150 mg/day)</td>
</tr>
<tr>
<td></td>
<td>400 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day)</td>
</tr>
</tbody>
</table>

**Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate** (see section 4.5), depending on original dose of lamotrigine:

This dosage regimen should be used when the following are added without valproate: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir.

<table>
<thead>
<tr>
<th></th>
<th>200 mg/day</th>
<th>200 mg/day</th>
<th>300 mg/day</th>
<th>400 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>225 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td></td>
<td>100 mg/day</td>
<td>100 mg/day</td>
<td>150 mg/day</td>
<td>200 mg/day</td>
</tr>
</tbody>
</table>

**Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):**
| This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added | Maintain target dose achieved in dose escalation (200 mg/day; dose range 100-400 mg/day) |

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.

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

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

**General dosing recommendations for lamotrigine in special patient populations**

**Women taking hormonal contraceptives**
The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

**Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation**
The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

**Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking inducers of lamotrigine glucuronidation**
The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the
Starting lamotrigine in patients already taking hormonal contraceptives
Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation
Adjustment to the recommended maintenance dose of lamotrigine may not be required.

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Elderly (above 65 years)
No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population (see section 5.2).

Renal impairment
Caution should be exercised when administering 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).

Hepatic impairment
Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

4.4 Special warnings and precautions for use
Skin rash
There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self
limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life threatening skin rashes including Stevens Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

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

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

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

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

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

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

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 (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including lamotrigine. Therefore patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

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

Effects of lamotrigine on hormonal contraceptive efficacy

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine has a slight inhibitory effect on dihydrofolate acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal failure

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

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

Development in children
There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.

Precautions relating to epilepsy
As with other AEDs, abrupt withdrawal of 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 two weeks.

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

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

Myoclonic seizures may be worsened by lamotrigine.

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

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

Precautions relating to bipolar disorder

Children and adolescents below 18 years
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

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

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

**Table 6: Effects of other medicinal products on glucuronidation of lamotrigine**

<table>
<thead>
<tr>
<th>Medicinal products that significantly inhibit glucuronidation of lamotrigine</th>
<th>Medicinal products that significantly induce glucuronidation of lamotrigine</th>
<th>Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Felbamate</td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td></td>
<td>Levetiracetam</td>
</tr>
</tbody>
</table>
**Interactions involving antiepileptic drugs**

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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

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

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

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

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

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.
In a study of patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

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

Interactions involving other psychoactive agents

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

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

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

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

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

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

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, dosing with 30 μg ethinyloestradiol/150 μg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during cotherapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined oral contraceptive
A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products
In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

Data from in vitro assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is a more potent in vitro inhibitor of OCT 2 than cimetidine, with IC₅₀ values of 53.8 µM and 186 µM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

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

4.6 Fertility, Pregnancy and lactation
Risk related to antiepileptic drugs in general.
Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

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

Risk related to lamotrigine.
Pregnancy
Postmarketing data from several prospective pregnancy registers have documented outcomes in over 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall these data do not suggest a substantial increase in the risk for congenital malformations, although data are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).
If therapy with lamotrigine is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase and could therefore theoretically lead to an increased risk of embryofoetal damage by reducing folic acid levels (see section 4.4). Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

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

**Lactation**

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother’s. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. Among a limited group of exposed infants, no adverse effects were observed.

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

**Fertility**

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

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

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

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

### 4.8 Undesirable effects

The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine.

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

- **Very common** ($\geq 1/10$),
- **Common** ($\geq 1/100, <1/10$),
- **Uncommon** ($\geq 1/1000, <1/100$),
- **Rare** ($\geq 1/10,000, <1/1000$),
- **Very rare** ($<1/10,000$),
- **Not known** (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Epilepsy**
Blood and lymphatic system disorders
Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis.

Frequency not known: lymphadenopathy

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

Immune system disorders
Very rare: hypersensitivity syndrome** (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi-organ failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Psychiatric disorders
Common: aggression, irritability.
Very rare: confusion, hallucinations, tics.

Nervous system disorders
During monotherapy clinical trials:

Very common: headache.
Common: somnolence, dizziness, tremor, insomnia.
Uncommon: ataxia.
Rare: nystagmus.

During other clinical experience:

Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

Frequency not known: aseptic meningitis

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.

Eye disorders
During monotherapy clinical trials:

Uncommon: diplopia, blurred vision.

During other clinical experience:

Rare: conjunctivitis.

Gastrointestinal disorders
During monotherapy clinical trials:

Common: nausea, vomiting, diarrhoea.
**Hepato-biliary disorders**

Very rare: hepatic failure, hepatic dysfunction, increased liver function tests.

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

**Skin and subcutaneous tissue disorders**

Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

In double-blind, adjunctive clinical trials in adults, 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).

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

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

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

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

**Musculoskeletal and connective tissue disorders**

Very rare: lupus-like reactions.

**General disorders and administration site conditions**

Common: tiredness.

**Bipolar Disorder**

The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

**Nervous system disorders**

During bipolar disorder clinical trials:

- Very common: headache.
- Common: agitation, somnolence, dizziness.

**Gastrointestinal disorders**

During bipolar disorder clinical trials:

- Common: dry mouth

**Skin and subcutaneous tissue disorders**

During bipolar disorder clinical trials:

- Very common: skin rash.
- Rare: Stevens–Johnson Syndrome.
When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Musculoskeletal and connective tissue disorders
During bipolar disorder clinical trials:

Common: arthralgia.

General disorders and administration site conditions
During bipolar disorder clinical trials:

Common: pain, back pain.

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

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antiepileptics, ATC Code: N03AX09

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

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

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

In another study, single oral doses of 600mg 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 150mg and 300mg did not differ from placebo.

Clinical efficacy and safety in children aged 1 to 24 months
The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase.
(for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, CI95% -2.6% < > 50.2%, p=0.07.

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

Clinical efficacy and safety in Lennox-Gastaut syndrome
There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

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

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

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

<table>
<thead>
<tr>
<th>‘Proportion’ of patients being event free at week 76</th>
<th>Study SCAB2003</th>
<th>Study SCAB2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criterion</td>
<td>Bipolar I</td>
<td>Bipolar I</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Intervention free</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
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<tr>
<td>p-value Log rank test</td>
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<tr>
<td></td>
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<td>0.023</td>
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<td>0.04</td>
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<tr>
<td>Depression free</td>
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<td></td>
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<tr>
<td>Free of mania</td>
<td>0.70</td>
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<td></td>
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<td>0.280</td>
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<td>0.006</td>
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</tbody>
</table>

In supportive analyses of time to first depressive episode and time to first manic/hypomorphic or mixed episode, the lamotrigine-treated patients had significantly longer times to first depressive episode than placebo patients, and the treatment difference with respect to time to manic/hypomorphic or mixed episodes was not statistically significant.
The efficacy of lamotrigine in combination with mood stabilisers has not been adequately studied.

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

### 5.2 Pharmacokinetic properties

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

**Distribution**
Binding to plasma proteins is about 55%. It is very unlikely that displacement from plasma proteins would result in toxicity.

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

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

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

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

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

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

**Special patient populations**

**Children**
Clearance adjusted for bodyweight is higher in children aged 12 years and under 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 drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see 4.2 Posology and method of administration).
Infants aged 2 to 26 months
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher Cmax levels are likely to be observed in some children with a body weight below 10 kg.

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

Renal impairment
Twelve volunteers with chronic renal failure and another six individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient’s concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

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

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

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

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

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

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

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC50 was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section 5.1).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycollate

Iron oxide yellow (E172)

Maize starch

Magnesium stearate

6.2 Incompatibilities
None reported.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister strips comprising PVC/Aluminium foil enclosed in an outer carton. Pack sizes of 21, 28, 42, 56 or 100 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/04/2012

10 DATE OF REVISION OF THE TEXT
18/04/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 200 mg Tablets.

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Lamotrigine 200 mg Tablets are yellow, capsule shaped tablets with “200” on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy

Adolescents aged 13 years and above
Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.

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

Children and adolescents aged 2 to 12 years
Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

Monotherapy of typical absence seizures.

Bipolar disorder

Adults aged 18 years and above
Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

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

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

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

Restarting Therapy
Prescribers should assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued lamotrigine 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.
It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

**Epilepsy**

The recommended dose escalation and maintenance doses for adults and adolescents aged 13 years and above (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).

When concomitant AEDs are withdrawn or other AEDs/medicinal products are added on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5).

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/day (once a day)</td>
<td>25 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td></td>
</tr>
<tr>
<td>50 mg/day (once a day)</td>
<td>50 mg/day (once a day)</td>
<td>To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved</td>
<td></td>
</tr>
<tr>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td>500 mg/day has been required by some patients to achieve desired response</td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with valproate regardless of any concomitant medicinal products</td>
<td>12.5 mg/day (given as 25 mg on alternate days)</td>
<td>25 mg/day (once a day)</td>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td>To achieve maintenance, doses may be increased by maximum of 25 - 50 mg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>700 mg/day has been required by some patients to achieve desired response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used without valproate but with: phenytoin carbamazepine phenobarbitone primidone rifampicin lopinavir/ritonavir</td>
<td>50 mg/day (once a day)</td>
<td>100 mg/day (two divided doses)</td>
<td>200 – 400 mg/day (two divided doses)</td>
</tr>
<tr>
<td></td>
<td>To achieve maintenance, doses may be increased by maximum of 100 mg every one to two weeks until optimal response is achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>700 mg/day has been required by some patients to achieve desired response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/day (once a day)</td>
<td>0.3 mg/kg/day (once a day or two divided doses)</td>
<td>0.6 mg/kg/day (once a day or two divided doses)</td>
<td>1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved.</td>
</tr>
<tr>
<td>50 mg/day (once a day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 – 200 mg/day (once a day or two divided doses)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy of typical absence seizures:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.15 mg/kg/day* (once a day)</td>
<td>0.3 mg/kg/day (once a day)</td>
<td>1 – 5 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 mg/kg/day (two divided doses)</td>
<td>1.2 mg/kg/day (two divided doses)</td>
<td>5 – 15 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 mg/kg/day (two divided doses)</td>
<td>1.2 mg/kg/day (two divided doses)</td>
<td>5 – 15 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day</td>
</tr>
</tbody>
</table>

*Recommended dose range for adjunctive therapy with valproate.

**Note:** The treatment regimen should be adjusted according to individual patient response and tolerability, and should be reviewed at regular intervals.
Adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td>Doses in the range 100 - 400 mg/day used in clinical trials.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive therapy WITH valproate</strong> (inhibitor of lamotrigine glucuronidation – see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

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

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

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

**Children below 2 years**

There are limited data on the efficacy and safety of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see section 4.4). There are no data in children below 1 month of age. Thus lamotrigine is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2.

**Bipolar disorder**

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5</th>
<th>Target Stabilisation Dose (Week 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy with lamotrigine OR adjunctive therapy WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation</strong> (see section 4.5):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation</td>
<td>25 mg/day (once a day)</td>
<td>50 mg/day (once a day or two divided doses)</td>
<td>100 mg/day (once a day or two divided doses)</td>
<td>200 mg/day - usual target dose for optimal response (once a day or two divided doses)</td>
</tr>
<tr>
<td>Doses in the range 100 - 400 mg/day used in clinical trials.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This dosage regimen should be used with valproate regardless of any concomitant medicinal products

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Efficacy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg/day (given as 25 mg on alternate days)</td>
<td>25 mg/day (once a day)</td>
</tr>
</tbody>
</table>
| Maximum dose of 200 mg/day can be used depending on clinical response.

Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):

This dosage regimen should be used without valproate but with:
- phenytoin
- carbamazepine
- phenobarbitone
- primidone
- rifampicin
- lopinavir/ritonavir.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Efficacy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/day (once a day)</td>
<td>100 mg/day (two divided doses)</td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

* The Target stabilisation dose will alter depending on clinical response

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

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to withdrawal)</th>
<th>Week 1 (beginning with withdrawal)</th>
<th>Week 2</th>
<th>Week 3 onwards *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When valproate is withdrawn, double the stabilisation dose, not exceeding an increase of more than 100 mg/week</td>
<td>100 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day) (two divided doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg/day</td>
<td>300 mg/day</td>
<td>400 mg/day</td>
<td>Maintain this dose (400 mg/day)</td>
</tr>
</tbody>
</table>

| Withdrawal of inducers of lamotrigine glucuronidation (see section 4.5), depending on original dose of lamotrigine: |
| This dosage regimen should be used when the following are withdrawn: phenytoin |
| 400 mg/day | 400 mg/day | 300 mg/day | 200 mg/day |
| 300 mg/day | 300 mg/day | 225 mg/day | 150 mg/day |
carbamazepine  
phenobarbitone  
primidone  
rifampicin  
lopinavir/ritonavir

<table>
<thead>
<tr>
<th>Withdrawal of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5):</th>
</tr>
</thead>
<tbody>
<tr>
<td>This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are withdrawn.</td>
</tr>
<tr>
<td>Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 - 400 mg/day)</td>
</tr>
</tbody>
</table>

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.

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

<table>
<thead>
<tr>
<th>Table 5: Adults aged 18 years and above - adjustment of lamotrigine daily dosing following the addition of other medicinal products in treatment of bipolar disorder</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Current lamotrigine stabilisation dose (prior to addition)</th>
<th>Week 1 (beginning with addition)</th>
<th>Week 2</th>
<th>Week 3 onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5), depending on original dose of lamotrigine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg/day</td>
<td>100 mg/day</td>
<td>Maintain this dose (100 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg/day</td>
<td>150 mg/day</td>
<td>Maintain this dose (150 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/day</td>
<td>200 mg/day</td>
<td>Maintain this dose (200 mg/day)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate (see section 4.5), depending on original dose of lamotrigine: |
|---|---|---|---|
| This dosage regimen should be used when the following are added without valproate: phenytoin  carbamazepine  phenobarbitone  primidone  rifampicin  lopinavir/ritonavir. |
| 200 mg/day | 200 mg/day | 300 mg/day | 400 mg/day |
| 150 mg/day | 150 mg/day | 225 mg/day | 300 mg/day |
| 100 mg/day | 100 mg/day | 150 mg/day | 200 mg/day |

| Addition of medicinal products that do NOT significantly inhibit or induce lamotrigine glucuronidation (see section 4.5): |
|---|---|---|---|---|
| 200 mg/day | 200 mg/day | 150 mg/day | 100 mg/day |
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added.

Maintain target dose achieved in dose escalation (200 mg/day; dose range 100–400 mg/day)

In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate, should be used.

**Discontinuation of Lamotrigine in patients with bipolar disorder**

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

**Children and adolescents below 18 years**

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

**General dosing recommendations for lamotrigine in special patient populations**

**Women taking hormonal contraceptives**

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

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

The maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold (see sections 4.4 and 4.5). It is recommended that from the time that the hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods; see sections 4.4 and 4.5).

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

The maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50% (see sections 4.4 and 4.5). It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the
Starting lamotrigine in patients already taking hormonal contraceptives
Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation
Adjustment to the recommended maintenance dose of lamotrigine may not be required.

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

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

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed (see section 4.5).

Elderly (above 65 years)
No dosage adjustment from the recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly adult population (see section 5.2).

Renal impairment
Caution should be exercised when administering 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).

Hepatic impairment
Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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

4.4 Special warnings and precautions for use
Skin rash
There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine
have also been reported. These have included potentially life threatening skin rashes including Stevens Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

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

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

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

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

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

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that lamotrigine not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefit clearly outweighs the risk.

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 (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Clinical worsening and suicide risk
Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder,
including lamotrigine. Therefore patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Hormonal contraceptives

**Effects of hormonal contraceptives on lamotrigine efficacy**

The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure control. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example “pill-free week”), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

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

**Effects of lamotrigine on hormonal contraceptive efficacy**

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal preparations with lamotrigine cannot be excluded. Therefore patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

**Dihydrofolate reductase**

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy (see section 4.6). However, during prolonged human dosing, lamotrigine did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

**Renal failure**

In single dose studies in subjects with end stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.
Patients taking other preparations containing lamotrigine
Lamotrigine should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

Development in children
There are no data on the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural developments in children.

Precautions relating to epilepsy
As with other AEDs, abrupt withdrawal of 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 two weeks.

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

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

Myoclonic seizures may be worsened by lamotrigine.

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

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

Precautions relating to bipolar disorder

Children and adolescents below 18 years
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

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

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

Table 6: Effects of other medicinal products on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Medicinal products that significantly inhibit glucuronidation of lamotrigine</th>
<th>Medicinal products that significantly induce glucuronidation of lamotrigine</th>
<th>Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Phenytoin</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Felbamate</td>
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<tr>
<td>Phenobarbital</td>
<td>Gabapentin</td>
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<tr>
<td>Primidone</td>
<td>Levetiracetam</td>
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<tr>
<td>Rifampicin</td>
<td>Pregabalin</td>
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</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Topiramate</td>
<td></td>
</tr>
</tbody>
</table>
*For dosing guidance (see section 4.2)

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

**Interactions involving antiepileptic drugs**

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes induce the glucuronidation of lamotrigine and enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

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

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

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

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

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

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.
In a study of patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

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

Interactions involving other psychoactive agents

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

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

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

Multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

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

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

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, dosing with 30 μg ethinylöstradiol/150 μg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylöstradiol component of a combined oral contraceptive
pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products
In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the appropriate treatment regimen should be used (see section 4.2).

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

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

Data from in vitro assessment demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is a more potent in vitro inhibitor of OCT 2 than cimetidine, with IC₅₀ values of 53.8 µM and 186 µM, respectively. Co-administration of lamotrigine with renally excreted medicinal products which are substrates of OCT2 (e.g. metformin, gabapentin and varenicline) may result in increased plasma levels of these drugs.

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

4.6 Fertility, Pregnancy and lactation

Risk related to antiepileptic drugs in general.

Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

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

Risk related to lamotrigine.

Pregnancy
Postmarketing data from several prospective pregnancy registers have documented outcomes in over 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall these data do not suggest a substantial increase in the risk for congenital malformations, although data are still too limited to exclude a moderate increase in the risk of oral clefts. Animal studies have shown developmental toxicity (see section 5.3).
If therapy with lamotrigine is considered necessary during pregnancy, the lowest possible therapeutic dose is recommended.

Lamotrigine has a slight inhibitory effect on dihydrofolate acid reductase and could therefore theoretically lead to an increased risk of embryofetal damage by reducing folic acid levels (see section 4.4). Intake of folic acid when planning pregnancy and during early pregnancy may be considered.

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

**Lactation**
Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother’s. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur. Among a limited group of exposed infants, no adverse effects were observed.

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

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

### 4.7 Effects on ability to drive and use machines
As there is individual variation in response to all AED therapy, patients taking lamotrigine to treat epilepsy should consult their physician on the specific issues of driving and epilepsy.

No studies on the effects on the ability to drive and use machines have been performed. Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor co-ordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine adverse reactions of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

### 4.8 Undesirable effects
The undesirable effects have been divided into epilepsy and bipolar specific sections based on the data currently available. However, both sections should be consulted when considering the overall safety profile of lamotrigine.

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

- **Very common (≥1/10),**
- **Common (≥1/100, <1/10),**
- **Uncommon (≥1/1000, <1/100),**
- **Rare (≥1/10,000, <1/1000),**
- **Very rare (<1/10,000),**
- **Not known (cannot be estimated from the available data).**

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Epilepsy

**Blood and lymphatic system disorders**

Very rare: haematological abnormalities including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis.

Frequency not known: lymphadenopathy

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

**Immune system disorders**

Very rare: hypersensitivity syndrome** (including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver, disseminated intravascular coagulation, multi-organ failure).

**Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

**Psychiatric disorders**

Common: aggression, irritability.

Very rare: confusion, hallucinations, tics.

**Nervous system disorders**

During monotherapy clinical trials:

Very common: headache.

Common: somnolence, dizziness, tremor, insomnia.

Uncommon: ataxia.

Rare: nystagmus.

During other clinical experience:

Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

Frequency not known: aseptic meningitis

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.

**Eye disorders**

During monotherapy clinical trials:

Uncommon: diplopia, blurred vision.

During other clinical experience:

Rare: conjunctivitis.

**Gastrointestinal disorders**

During monotherapy clinical trials:

Common: nausea, vomiting, diarrhoea.
**Hepato-biliary disorders**
Very rare: hepatic failure, hepatic dysfunction, increased liver function tests.

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

**Skin and subcutaneous tissue disorders**
Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

In double-blind, adjunctive clinical trials in adults, 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).

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

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

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

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

**Musculoskeletal and connective tissue disorders**
Very rare: lupus-like reactions.

**General disorders and administration site conditions**
Common: tiredness.

**Bipolar Disorder**

The undesirable effects below should be considered alongside those seen in epilepsy for an overall safety profile of lamotrigine.

**Nervous system disorders**
During bipolar disorder clinical trials:

Very common: headache.
Common: agitation, somnolence, dizziness.

**Gastrointestinal disorders**
During bipolar disorder clinical trials:
Common: dry mouth

**Skin and subcutaneous tissue disorders**
During bipolar disorder clinical trials:

Very common: skin rash.
Rare: Stevens–Johnson Syndrome.
When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Musculoskeletal and connective tissue disorders
During bipolar disorder clinical trials:

Common: arthralgia.

General disorders and administration site conditions
During bipolar disorder clinical trials:

Common: pain, back pain.

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

Treatment
In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20% of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antiepileptics, ATC Code: N03 A X09

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

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

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

In another study, single oral doses of 600mg 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 150mg and 300mg did not differ from placebo.

Clinical efficacy and safety in children aged 1 to 24 months
The efficacy and safety of adjunctive therapy in partial seizures in patients aged 1 to 24 months has been evaluated in a small double-blind placebo-controlled withdrawal study. Treatment was initiated in 177 subjects, with a dose titration schedule similar to that of children aged 2 to 12 years. Lamotrigine 2 mg tablets are the lowest strength available, therefore the standard dosing schedule was adapted in some cases during the titration phase.
(for example, by administering a 2 mg tablet on alternate days when the calculated dose was less than 2 mg). Serum levels were measured at the end of week 2 of titration and the subsequent dose either reduced or not increased if the concentration exceeded 0.41 µg/mL, the expected concentration in adults at this time point. Dose reductions of up to 90% were required in some patients at the end of week 2. Thirty-eight responders (> 40% decrease in seizure frequency) were randomised to placebo or continuation of lamotrigine. The proportion of subjects with treatment failure was 84% (16/19 subjects) in the placebo arm and 58% (11/19 subjects) in the lamotrigine arm. The difference was not statistically significant: 26.3%, C195% -2.6% < > 50.2%, p=0.07.

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

Clinical efficacy and safety in Lennox-Gastaut syndrome
There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

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

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

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

<table>
<thead>
<tr>
<th>‘Proportion’ of patients being event free at week 76</th>
<th>Study SCAB2003 Bipolar I</th>
<th>Study SCAB2006 Bipolar I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criterion</td>
<td>Major depressive episode</td>
<td>Major manic episode</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lithium</td>
<td>Placebo</td>
</tr>
<tr>
<td>Intervention free</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>Depression free</td>
<td>0.51</td>
<td>0.46</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.047</td>
<td>0.209</td>
</tr>
<tr>
<td>Free of mania</td>
<td>0.70</td>
<td>0.86</td>
</tr>
<tr>
<td>p-value Log rank test</td>
<td>0.339</td>
<td>0.026</td>
</tr>
</tbody>
</table>

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

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

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

5.2 Pharmacokinetic properties

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

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

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

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

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

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

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

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

Special patient populations

Children
Clearance adjusted for bodyweight is higher in children aged 12 years and under 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 drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see 4.2 Posology and method of administration).
Infants aged 2 to 26 months
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher Cmax levels are likely to be observed in some children with a body weight below 10 kg.

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

Renal impairment
Twelve volunteers with chronic renal failure and another six individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean clearances were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis) and 1.57 mL/min/kg (during haemodialysis), compared with 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient’s concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

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

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

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

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

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

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

Lamotrigine caused a dose-related inhibition of the hERG channel tail current in human embryonic kidney cells. The IC50 was approximately nine-times above the maximum therapeutic free concentration. Lamotrigine did not cause QT prolongation in animals at exposures up to approximately two-times the maximum therapeutic free concentration. In a clinical study, there was no clinically significant effect of lamotrigine on QT interval in healthy adult volunteers (see section 5.1).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycollate

Iron oxide yellow (E172)

Maize starch

Magnesium stearate

6.2 Incompatibilities
None reported.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister strips comprising PVC/Aluminium foil enclosed in an outer carton. Pack sizes of 21, 28, 42, 56 or 100 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/04/2012

10 DATE OF REVISION OF THE TEXT
18/04/2012
PATIENT INFORMATION LEAFLET

LAMOTRIGINE

25 mg, 50 mg, 100 mg and 200 mg tablets (Lamictal)

This leaflet is for 25 mg, 50 mg, 100 mg and 200 mg tablets, which are referred to as Lamotrigine Tablets throughout this leaflet.

1. WHAT LAMOTRIGINE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in this product is lamotrigine, which belongs to a group of medicines called antiepileptic drugs. It is used to treat conditions - epilepsy and bipolar disorder.

Lamotrigine Tablets may be used in the following conditions:
- For adults and children aged 13 years and over: Lamotrigine Tablets may be used on their own or with other medicines, to treat epilepsy. Lamotrigine Tablets can also be used with other medicines to treat the symptoms that occur with a condition called Lennox-Gastaut syndrome.
- For children aged between 2 and 12 years, Lamotrigine Tablets can be used with other medicines, to treat those conditions. It can be used on its own to treat a type of epilepsy called focal seizures (partial seizures).

Before you take Lamotrigine Tablets, read the information leaflet to ensure that you are not allergic to any of the ingredients. If you are allergic to any of the ingredients mentioned, please do not take Lamotrigine Tablets.

2. BEFORE YOU TAKE LAMOTRIGINE TABLETS

Do not take Lamotrigine Tablets if:
- You have had an allergic reaction to lamotrigine, or any of the other ingredients in Lamotrigine Tablets. These are listed in section 6. Further information.

3. HOW TO TAKE LAMOTRIGINE TABLETS

Taking the tablets:
- Take the tablets by mouth. Do not crush or break them. Do not chew them.

The tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg tablets. Take the dosage that is prescribed by your doctor. The dosage may be increased gradually over 1 to 4 weeks, or your doctor may prescribe a higher dose on the first day.

How much lamotrigine to take:
- The usual starting dose is 25 mg to 50 mg once daily. The dose may be increased gradually over 1 to 4 weeks. Your doctor may prescribe a higher dose on the first day.

If you miss a dose:
- Take it as soon as you remember. If you do not remember until the next day, carry on with your normal dose.

If you need to stop taking Lamotrigine Tablets:
- Talk to your doctor before stopping. It is important not to stop taking this medicine suddenly as this can cause seizures.

In case of overdose:
- Keep all medicines out of the reach of children.

Store:
- Store in a dry place. Do not store in the bathroom.

Disposing of unused medicines:
- Do not flush unused medicines down the toilet. Take them to a pharmacy for disposal.

Further information:
- Your doctor may also give you additional information or advice about lamotrigine.

4. POSSIBLE SIDE EFFECTS

The most common side effects are:
- A small number of people taking lamotrigine may have seizures (fits) or feel dizzy. This is more likely if you are starting lamotrigine tablets.
- A small number of people may develop nervousness, anxiety, or agitation. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop unusual movements of their body. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop unusual movements of their limbs. This may happen during the first few weeks of taking lamotrigine tablets.

5. WHAT TO DO IF YOU EXPERIENCE SEVERE SIDE EFFECTS

If you experience any of the following side effects, stop taking Lamotrigine Tablets and contact your doctor immediately:
- A small number of people may develop abnormal blood counts. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop swelling of the lips, tongue, or throat. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop unusual movements of their limbs. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop unusual movements of the body. This may happen during the first few weeks of taking lamotrigine tablets.

If you experience any of the following side effects, you should also contact your doctor:
- A small number of people may develop unusual movements of the body. This may happen during the first few weeks of taking lamotrigine tablets.

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- A small number of people may develop unusual movements of the body. This may happen during the first few weeks of taking lamotrigine tablets.

6. ADDITIONAL INFORMATION

If you experience any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

7. OVERDOSAGE

If you suspect an overdose, please seek medical advice immediately.

8. LEGAL INFORMATION

This leaflet is for lomotrigine tablets, which are referred to as Lamotrigine Tablets throughout this leaflet.

9. PATIENT INFORMATION LEAFLET

LAMOTRIGINE

25 mg, 50 mg, 100 mg and 200 mg tablets (Lamictal)

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- For children aged between 2 and 12 years, Lamotrigine Tablets can be used with other medicines, to treat those conditions. It can be used on its own to treat a type of epilepsy called focal seizures (partial seizures).

Before you take Lamotrigine Tablets, read the information leaflet to ensure that you are not allergic to any of the ingredients. If you are allergic to any of the ingredients mentioned, please do not take Lamotrigine Tablets.

2. BEFORE YOU TAKE LAMOTRIGINE TABLETS

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- You have had an allergic reaction to lamotrigine, or any of the other ingredients in Lamotrigine Tablets. These are listed in section 6. Further information.

3. HOW TO TAKE LAMOTRIGINE TABLETS

Taking the tablets:
- Take the tablets by mouth. Do not crush or break them. Do not chew them.

The tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg tablets. Take the dosage that is prescribed by your doctor. The dosage may be increased gradually over 1 to 4 weeks, or your doctor may prescribe a higher dose on the first day.

How much lamotrigine to take:
- The usual starting dose is 25 mg to 50 mg once daily. The dose may be increased gradually over 1 to 4 weeks. Your doctor may prescribe a higher dose on the first day.

If you miss a dose:
- Take it as soon as you remember. If you do not remember until the next day, carry on with your normal dose.

If you need to stop taking Lamotrigine Tablets:
- Talk to your doctor before stopping. It is important not to stop taking this medicine suddenly as this can cause seizures.

In case of overdose:
- Keep all medicines out of the reach of children.

Store:
- Store in a dry place. Do not store in the bathroom.

Disposing of unused medicines:
- Do not flush unused medicines down the toilet. Take them to a pharmacy for disposal.

Further information:
- Your doctor may also give you additional information or advice about lamotrigine.

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- A small number of people may develop nervousness, anxiety, or agitation. This may happen during the first few weeks of taking lamotrigine tablets.
- A small number of people may develop unusual movements of their body. This may happen during the first few weeks of taking lamotrigine tablets.
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6. ADDITIONAL INFORMATION

If you experience any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

7. OVERDOSAGE

If you suspect an overdose, please seek medical advice immediately.

8. LEGAL INFORMATION

This leaflet is for lomotrigine tablets, which are referred to as Lamotrigine Tablets throughout this leaflet.
UKPAR Lamotrigine 25, 50, 100 and 200mg Tablets

For children aged 2 to 12 years, the effective dose depends on their body weight—usually, it’s between 1 mg and 15 mg for each kilogram of the child’s weight, up to a maximum of 400 mg daily.

How to take your dose of Lamotrigine Tablets
Take your dose of Lamotrigine Tablets morning or before a day, as your doctor advises. You can take with or without food.

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

- Take your tablets whole. Don’t break, chew or divide them.
- Always take the full dose that your doctor has prescribed. Never take only part of a tablet.

If you’re taking more Lamotrigine Tablets than you should
If you take too much Lamotrigine Tablets
- Contact a doctor or pharmacist immediately. If possible, show them the Lamotrigine Tablets packet.

Someone who has taken too much lamotrigine may have any of these symptoms:
- marked, uncontrollable eye movements (mydriasis)
- clumsiness and lack of co-ordination, affecting their balance (ataxia)
- loss of consciousness or coma

If you forget to take Lamotrigine Tablets
Don’t take extra tablets or a double dose to make up for a forgotten dose.

If you have missed taking a dose of Lamotrigine Tablets
Ask your doctor for advice on how to start taking it again. It’s important that you do this.

Don’t stop taking Lamotrigine Tablets without advice
Take Lamotrigine Tablets for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

If you are taking Lamotrigine Tablets for epilepsy
Lamotrigine Tablets may take some time to work, so you are unlikely to feel better straight away. If you stop taking Lamotrigine Tablets, your dose will not be reduced gradually. But you should still talk to your doctor first, if you want to stop taking Lamotrigine Tablets.

4. POSSIBLE SIDE EFFECTS

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

Allergic reaction or potentially serious skin reactions: get a doctor’s help straight away.

A small number of people taking Lamotrigine Tablets get an allergic reaction or potentially serious skin reaction, which may develop into more serious and even life-threatening problems if they are not treated.

These symptoms are more likely to happen during the first few months of treatment with Lamotrigine Tablets, especially if you start on too high a dose or if your dose is increased too quickly, or if you’re taking Lamotrigine Tablets with another medicine called lithium. Some of the symptoms are more common in children, so parents should be especially careful to watch out for them.

Symptoms of these reactions include:
- skin rash or redness, which may develop into severe skin reactions including widespread rash with blisters and peeling skin, particularly occurring around the face, eyes, and mouth (Steven-Johnson syndrome), or exfoliating peeling of the skin (more than 30% of the body surface - toxic epidermal necrolysis)
- a sore mouth or lips
- a high temperature (fever), flu-like symptoms or diarrhoea
- swelling around the face or enlargement of lymph glands in the neck, arm, or groin
- unexplained bleeding or bruising, or your fingers turning blue
- a sore throat or more infections (such as coughs) than usual

In most cases, these symptoms will be signs of less serious side effects that you must be aware that they are potentially serious and can develop into more serious problems, such as organ failure. If they are not treated, if you notice any of these symptoms:
- Contact a doctor immediately: Your doctor may decide to carry out tests on your liver, kidneys or blood, and may tell you to stop taking Lamotrigine Tablets.

Very common side effects:
These may affect more than 1 in 10 people:
- feeling depressed
- feeling nervous
- feeling sleepy or drowsy
- clumsiness and lack of coordination (ataxia)
- double vision or blurred vision
- feeling sick (nausea) or being sick (vomiting)
- skin rash

Common side effects:
These may affect up to 1 in 10 people:
- aggression or irritability
- rapid, uncontrollable eye movements (mydriasis)
- shaking or tremors
- feeling sick or more tired
- blurred vision
- dry mouth
- feeling dizzy
- pain in your back, neck, or back

Rarer side effects:
These may affect up to 1 in 1000 people:
- dry eyes, with discharge and redness (conjunctivitis)
- rash (severe skin reaction; Stevens-Johnson syndrome; see also the information at the beginning of Section 4)

Very rare side effects:
These may affect up to 1 in 10,000 people:
- hallucinations (seeing or hearing things that aren’t really there)
- convulsions or irritation
- feeling weak or unsteady when you move about
- uncontrolled body movements (tics), uncontrolled muscle spasms affecting the eyes, head and torso (torticollis), or other unusual body movements such as jerking, shaking, twitching
- a serious skin reaction (see epidermal necrolysis; see also the information at the beginning of Section 4)
- changes in behaviour, especially among children younger than 12 years or teenagers
- a slower rate of speech or more difficulty in talking
- changes in liver function, which will show up in blood tests, or liver failure
- changes which may show up in blood tests – including reduced numbers of white blood cells (leucopenia), reduced numbers of white blood cells (thrombocytopenia), reduced number of platelets (thrombocytopenia), reduced number of all these types of cells (pancytopenia), and a disorder of the bone marrow called aplastic anaemia
- a serious, life-threatening blood disorder, which can cause unexpected bleeding or trouble with blood clotting (haemorrhagic purpura)
- high temperature (fever)
- swelling around the face (oedema) or easier bruising in the neck, arm, or groin (lymphadenopathy)
- in people who have already had Lamotrigine tablets, worsening of symptoms
- in a group of symptoms together including, fever, rash, vomiting, headache, stiff neck and extreme sensitivity to bright light. This may be caused by an inflammation of the membranes that cover the brain and spinal cord (meningitis)

Other side effects:
Other side effects have occurred in a small number of people but their exact frequency is unknown:
- a group of symptoms together including, fever, rash, vomiting, headache, stiff neck and extreme sensitivity to bright light. This may be caused by an inflammation of the membranes that cover the brain and spinal cord (meningitis). These symptoms usually disappear once treatment is stopped but if the symptoms continue or get worse contact your doctor.

If you notice any side effects:
If any of the side effects becomes severe or troublesome, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

5. HOW TO STORE LAMOTRIGINE TABLETS

Keep Lamotrigine Tablets out of the reach and sight of children.
Do not use Lamotrigine Tablets after the expiry date shown on the container, blister or bottle. The expiry date states the last day of that month.

Lamotrigine does not require any special storage conditions.

If you have any unwanted Lamotrigine Tablets, don’t dispose of them in your washbasin or household rubbish. Take them back to your pharmacist, who will dispose of them in a way that won’t harm the environment.

6. FURTHER INFORMATION

What Lamotrigine Tablets contain
The active ingredient is lamotrigine. Each tablet contains 25, 50, 100 or 200 mg of lamotrigine.

The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and iron oxide yellow (E 172).

What Lamotrigine Tablets look like and contents of the pack
Lamotrigine 25 mg, 50 mg and 100 mg Tablets are yellow, round tablets with "25", "50" or "100" on one side and a score line on the other. Lamotrigine 200 mg Tablets are yellow, capsule-shaped tablets with “200” on one side and a score line on the other.

Your medicine is available in packs of 21, 28, 42, 56, or 108 tablets (and all pack sizes may be marked).

Manufacturing Authorisation Holder
STC Pharmaceuticals Ltd, Orange House, 1–3 Hillview Road, Esher, Surrey, KT10 9HP

Manufacturers responsible for batch release: Newable Limited, 57 High Street, Oxted, Surrey, RH8 1DJ, UK

This leaflet was last revised in October 2011
Also contains lactose and maize starch.
For oral administration.
Use as directed by a doctor.
Please read the enclosed leaflet.
Store in the original package.
Keep out of reach and sight of children.

56 Tablets

Distributor:
Nordahl Ltd, 57 High Street, Oakham, Rutland, LE15 9LF.
PL 36390003431
MA Holder: STD Chemicals Ltd, Hidcote House,
Hidcote Road, Isher, Surrey, KT10 9NW.

Lamotrigine 50 mg Tablets
MA holder: STD Chemicals Ltd.
Code No: XX/DRUG/5/XXX

Lamotrigine 50 mg Tablets
MA holder: STD Chemicals Ltd.
Code No: XX/DRUG/5/XXX

Lamotrigine 50 mg Tablets
MA holder: STD Chemicals Ltd.
Code No: XX/DRUG/5/XXX
Lamotrigine 100 mg Tablets

Barcode

Also contains lactose and maize starch.
For oral administration.
Use as directed by a doctor.
Please read the enclosed leaflet.
Store in the original package.
Keep out of reach and sight of children.

Lamotrigine 100 mg Tablets

Each tablet contains 100 mg lamotrigine

56 Tablets

MA holder: STD Chemicals Ltd.
Code No.: XXXDRUG/XXX

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Code No.: XXXDRUG/XXX

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Code No.: XXXDRUG/XXX

MA holder: STD Chemicals Ltd.
Code No.: XXXDRUG/XXX