LAMOTRIGINE 2MG DISPERSIBLE TABLETS
(PL 20477/0011 and PL 20477/0021)

LAMOTRIGINE 5MG DISPERSIBLE TABLETS
(PL 20477/0012 and PL 20477/0022)

LAMOTRIGINE 25MG DISPERSIBLE TABLETS
(PL 20477/0013)

LAMOTRIGINE 50MG DISPERSIBLE TABLETS
(PL 20477/0014)

LAMOTRIGINE 100MG DISPERSIBLE TABLETS
(PL 20477/0015)

LAMOTRIGINE 200MG DISPERSIBLE TABLETS
(PL 20477/0020)

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Steps taken after authorisation – summary Page 13
Summary of Product Characteristics
Product Information Leaflet
Labelling
LAY SUMMARY

The MHRA today granted Kohne Pharma GmbH Marketing Authorisations (licences) for the medicinal products Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Dispersible Tablets. These are prescription-only medicines (POM) that act as anticonvulsants for the treatment of epilepsy.

Lamotrigine Tablets contain the active ingredient lamotrigine, which acts on voltage dependent sodium action potentials resulting in the decreased release of presynaptic glutamate.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Lamotrigine Dispersible Tablets outweigh the risks, hence Marketing Authorisations have been granted.
LAMOTRIGINE 2MG DISPERSIBLE TABLETS  
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LAMOTRIGINE 100MG DISPERSIBLE TABLETS  
(PL 20477/0015)

LAMOTRIGINE 200MG DISPERSIBLE TABLETS  
(PL 20477/0020)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>7</td>
</tr>
<tr>
<td>Clinical assessment (including statistical assessment)</td>
<td>8</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>11</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Lamotrigine 2, 5, 25, 50, 100 and 200mg Dispersible Tablets to Kohne Pharma GmbH (PL 20477/0011-5, 0020-22) on 2nd March 2007. The products are prescription-only medicines.

These are national abridged applications for lamotrigine tablets claiming essential similarity to the originator product, Lamictal Tablets (PL 00003/0272–0274 and 00003/0297) first licensed to The Wellcome Foundation Limited on 21st October 1991 and 19th February 1992, respectively.

The products contain the active ingredient lamotrigine, which is a treatment for epilepsy, either as monotherapy or as an adjunct to treatment with other antiepileptic agents for partial seizures, and primary and secondary generalised tonic-clonic seizures, and the treatment of seizures associated with Lennox-Gastaut syndrome.

These applications for Lamotrigine 2, 5, 25, 50, 100 and 200mg Dispersible Tablets were submitted at the same time and both depend on two bioequivalence studies, comparing the applicant’s 5mg and 200mg products with the Lamictal Tablets of the same strength. Consequently, all sections of this Scientific Discussion refer to all products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Lamotrigine

INN: Lamotrigine

Chemical Name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine

Molecular Formula: \( \text{C}_9\text{H}_7\text{Cl}_2\text{N}_5 \)

Structure:

![Molecular structure of Lamotrigine]

Molecular Weight: 256.09

CAS Number: 84057-84-1

Appearance: White to pale cream powder with no polymorphism or chirality/optical activity. It is very slightly soluble in water and slightly soluble in 0.1M HCl

Lamotrigine is not the subject of a British or European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance lamotrigine. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of analysis have been provided for any working standards used.

Batch analysis data are provided and comply with the proposed specification.

The active lamotrigine is packaged in a transparent, food-grade, polythene bag, placed inside a triple-laminated aluminium bag, which is then placed in a fibre board drum. Specifications for all packaging have been provided and all are suitable for use in storing pharmaceutical products. All packaging that comes into contact with the drug substance complies with European directives regarding suitability for contact with food.
Appropriate stability data have been generated supporting a retest period of 2 years.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of microcrystalline cellulose, cal carb 4450, crospovidone, povidone k30, water purified, aspartame, low-substituted hydroxypropyl cellulose, mixed berry flavour powder, magnesium stearate, colloidal anhydrous silica and talc. All excipients comply with their respective European Pharmacopoeia monographs, except cal carb 4450 and mixed berry flavour powder (which are controlled to suitable in-house specifications).

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical development**

A satisfactory development rationale has been provided for these products. Comparative dissolution profiles were shown for the proposed product versus the originator product.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided and are satisfactory.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on production-scale batches of each strength. The results appear satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The finished product is stored in either:

- 2mg strength: opaque high-density polyethylene bottles with a cap closure or lacquered aluminium/polyamide/polyvinylchloride blisters that are stored in cardboard boxes (in pack sizes of 28 or 30 tablets)
- 5mg strengths: lacquered aluminium/polyvinylchloride/polyvinylidene chloride blisters that are stored in cardboard boxes (in pack sizes of 28 or 30 tablets)
- 25mg, 50mg, 100mg and 200mg strengths: lacquered aluminium/polyamide/polyvinylchloride blisters or lacquered aluminium/polyvinylchloride/polyvinylidene chloride blisters that are stored in cardboard boxes (in pack sizes of 1, 2, 4, 7, 10, 14, 28, 30, 56, 98 and 100 tablets)

Bulk tablets are also stored in low-density polyethylene bags, containing five desiccant sachets, which are contained in a triple laminated bag, along with five more desiccant sachets before packing into the finished product packaging.

Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory.
The applicant has confirmed that all packaging that comes into direct contact with the drug product complies with European Directive 90/128/EEC with respect to their contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Batches of finished product manufactured at the proposed finished product manufacturer, using active substance from the proposed active substance manufacturer and in packaging proposed for marketing were placed on stability at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH.

Based on the results, a shelf-life of 2 years with the conditions ‘Store in original packaging’ has been set. An additional specification of ‘Do not store above 25°C’ has been set for the 25mg, 50mg, 100mg and 200mg strengths. These are satisfactory.

Suitable post approval stability commitments have been provided by the applicant, who will place the first three production-scale batches on stability.

**Bioequivalence**
Two bioequivalence studies were performed, one using the cross-reference product Lamictal Chewable Dispersible 5mg Tablets (GlaxoSmithKline, Germany) versus the applicant’s 5mg tablet strength, and another using the cross-reference product Lamictal 200mg Tablets (GlaxoSmithKline, Germany) versus the applicant’s 200mg tablet strength. Bioequivalence was shown between both strengths of proposed product and the originator products. Further details are given in the clinical assessment.

Certificates of analysis, including assay, dissolution and impurity profiles, are provided for the batches subjected to bioequivalence studies. These are satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications. The requirements for the proposed products to be generic medicinal products of the reference products have been met.
PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Lamictal 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Tablets (The Wellcome Foundation Limited, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
Two bioequivalence studies have been provided:

1. **Comparison of Lamotrigine Chewable Dispersible 5mg Tablets versus Lamictal Chewable Dispersible 5mg Tablets**
   The applicant has submitted a randomised, open-label, two-treatment, two-sequence, single-dose, crossover study comparing the bioavailability of test Lamotrigine Chewable Dispersible 5mg Tablets versus Lamictal Chewable Dispersible 5mg Tablets (GlaxoSmithKline, Germany) in healthy volunteers under fasted conditions.

   Blood samples were collected pre-dose and up to 72 hours post dose, followed by a 21-day washout period before the next treatment was administered. Pharmacokinetic parameters $AUC_{0-72}, C_{\text{max}}$ and $T_{\text{max}}$ were calculated.

   The main pharmacokinetic results for lamotrigine are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least Squares Means</th>
<th>Test/Ref. Ratio</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-72}$ (ng·hr/ml)</td>
<td>12116.11</td>
<td>11625.70</td>
<td>1.04</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>349.33</td>
<td>340.57</td>
<td>1.03</td>
</tr>
</tbody>
</table>

   **Ln-Transformed Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least Squares Means</th>
<th>Test/Ref. Ratio</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-72}$ (ng·hr/ml)</td>
<td>11804.42</td>
<td>11268.25</td>
<td>1.05</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>342.65</td>
<td>335.84</td>
<td>1.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$T_{\text{max}}$ (hour)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1.00</td>
</tr>
<tr>
<td>Reference</td>
<td>1.50</td>
</tr>
</tbody>
</table>

1. Least squares geometric means for ln-transformed data.
2. Test/Ref. Ratio calculated as Test mean divided by Reference mean.
3. Confidence interval on the ratio.
As the AUC-ratio 90% confidence interval of relative bioavailability lies within an acceptance range, it is concluded that bioequivalence has been demonstrated between the test and reference products in accordance with the CPMP criteria. Data have been provided that successfully shows that the German Lamictal product and the UK Lamictal product can be considered to be identical.

As the 2mg and 5mg products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the 2mg strength tablets.

### 2. Comparison of Lamotrigine Chewable Dispersible 200mg Tablets versus Lamictal 200mg Tablets

The applicant has submitted a randomised, open-label, two-treatment, two-sequence, single-dose, crossover study comparing the bioavailability of test Lamotrigine Chewable Dispersible 200mg Tablets versus Lamictal 200mg Tablets (GlaxoSmithKline, Germany) in healthy volunteers under fasted conditions.

Blood samples were collected pre-dose and up to 120 hours post dose, followed by a 20-day washout period before the next treatment was administered. Pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$, AUC$_{0-72}$ and AUC$_{0-\infty}$ were calculated.

The main pharmacokinetic results for lamotrigine are presented below:

<table>
<thead>
<tr>
<th>Test Drug (A)</th>
<th>Geometric Mean</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>3.0295</td>
<td>3.0929</td>
<td>0.6613</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours)</td>
<td>1.82</td>
<td>2.17</td>
<td>1.28</td>
<td>59</td>
<td>23</td>
</tr>
<tr>
<td>AUC$_{0-6}$ (μg.hr/ml)</td>
<td>117.5296</td>
<td>121.3581</td>
<td>30.7393</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (μg.hr/ml)</td>
<td>136.9411</td>
<td>145.1836</td>
<td>50.9303</td>
<td>35</td>
<td>23</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Drug (B)</th>
<th>Geometric Mean</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>2.8763</td>
<td>2.9042</td>
<td>0.4251</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (Hours)</td>
<td>2.46</td>
<td>3.00</td>
<td>0.91</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>AUC$_{0-6}$ (μg.hr/ml)</td>
<td>121.3990</td>
<td>125.6361</td>
<td>33.2120</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (μg.hr/ml)</td>
<td>136.1561</td>
<td>145.6864</td>
<td>52.0634</td>
<td>36</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Ratio (A/B)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>103.30%</td>
</tr>
<tr>
<td>AUC$_{0-6}$</td>
<td>97.07%</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>100.22%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>90% CI (Log transformed) Test and Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>99.45% to 111.91%</td>
</tr>
<tr>
<td>AUC$_{0-6}$</td>
<td>91.71% to 102.74%</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>96.41% to 104.17%</td>
</tr>
</tbody>
</table>
As the AUC-ratio 90% confidence interval of relative bioavailability lies within an acceptance range, it is concluded that bioequivalence has been demonstrated between the test and reference products in accordance with the CPMP criteria. Data have been provided that successfully shows that the German Lamictal product and the UK Lamictal product can be considered to be identical.

As the 25mg, 50mg, 100mg and 200mg products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength can be extrapolated to the 25mg, 50mg and 100mg strength tablets.

**EFFICACY**
No new data has been provided.

**SAFETY**
No new data has been provided. No new or unexpected safety issues have been raised during the bioequivalence study.

**EXPERT REPORTS**
A clinical expert report has been written by a suitably qualified person and is satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**
This is consistent with that for the reference products and is satisfactory.

**LABELLING**
These are satisfactory.

**APPLICATION FORMS (MAA)**
These are satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
These are consistent with those for the reference products and are satisfactory.

**DISCUSSION**
The applicant has satisfactorily demonstrated bioequivalence between the 5mg and 200mg strengths of test and originator products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the 2mg strength tablets, and the results of the 200mg strength tablets can be extrapolated to the 25mg, 50mg and 100mg strength tablets.

**MEDICAL CONCLUSION**
The bioequivalence study submitted has shown that these products can be considered as generic medicinal products to the originator products Lamictal Dispersible Tablets (GlaxoSmithKline, UK).

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Lamotrigine 2, 5, 25, 50, 100 and 200mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Lamotrigine 5mg Dispersible Tablets and Lamictal 5mg Dispersible Tablets, and Lamotrigine 200mg Dispersible Tablets and Lamictal 200mg Tablets. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the 2mg strength tablets, and the results of the 200mg strength tablets can be extrapolated to the 25mg, 50mg and 100mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for Lamictal tablets where necessary.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with lamotrigine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
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LAMOTRIGINE 5MG DISPERSIBLE TABLETS  
(PL 20477/0012 and PL 20477/0022)

LAMOTRIGINE 25MG DISPERSIBLE TABLETS  
(PL 20477/0013)

LAMOTRIGINE 50MG DISPERSIBLE TABLETS  
(PL 20477/0014)

LAMOTRIGINE 100MG DISPERSIBLE TABLETS  
(PL 20477/0015)

LAMOTRIGINE 200MG DISPERSIBLE TABLETS  
(PL 20477/0020)

**STEPS TAKEN FOR ASSESSMENT**

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<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 23rd December 2004</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 27th January 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 17th November 2005, and further information relating to the quality dossiers on 10th November 2005 and 18th May 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 17th November 2005 for the clinical sections, and again on 18th May 2006 and 24th November 2006 for the quality sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 2nd March 2007</td>
</tr>
</tbody>
</table>
LAMOTRIGINE 2MG DISPERSIBLE TABLETS
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(PL 20477/0015)

LAMOTRIGINE 200MG DISPERSIBLE TABLETS
(PL 20477/0020)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 2mg Dispersible Tablets

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

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Dispersible tablets.

Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, debossed with ‘LI’ on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy:
Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

4.2 Posology and method of administration
Administration
Lamotrigine tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

Dosage in monotherapy
Adults and children over 12 years (see Table 1)

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

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

Children aged 2 to 12 years
There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

Dosage in add-on therapy
Adults and children over 12 years (see Table 1)

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

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

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

Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100 - 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
<tr>
<td>Add-on therapy with valproate</td>
<td>12.5 mg (given 25 mg on</td>
<td>25 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td>regardless of any concomitant</td>
<td>alternate days)</td>
<td></td>
<td>To achieve manten</td>
</tr>
<tr>
<td>medications</td>
<td></td>
<td></td>
<td>nce, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
</tbody>
</table>
Add-on therapy without valproate

<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>Add-on therapy with valproate regardless of any other concomitant medication</td>
<td>0.15 mg/kg* (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

Add-on therapy without valproate

<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>This dosage regimen should be used with: phenytoin carbamazepine phenobarbital</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg</td>
</tr>
</tbody>
</table>
Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

* If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

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

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

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

Women and Hormonal Contraceptives (see sections 4.4 and 4.5)
(a) Starting lamotrigine in patients taking hormonal contraceptives
Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

Pregnancy and post-partum
Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

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

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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
• High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
• Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multigorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with Phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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>
<thead>
<tr>
<th>Drugs that significantly inhibit glucuronidation of lamotrigine</th>
<th>Drugs that significantly induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

**Interactions involving Oral Contraceptives**

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

**Effect of lamotrigine on oral contraceptives:**

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

**4.6 Pregnancy and lactation**

**Fertility**

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

**Teratogenicity**

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
<td>Liuops</td>
<td></td>
<td>Stevens Johnson syndrome</td>
<td>Lyell syndrome</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Aplastic anaemia agranulocytosis</td>
<td>Neutropenia</td>
<td>Leucopenia</td>
<td>Anaemia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Aggression</td>
<td>Confusion and Hallucinations</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>Increase in seizure</td>
<td>Dizziness</td>
<td>Insomnia</td>
<td>Tremor</td>
<td>Tics</td>
</tr>
</tbody>
</table>

22
Ataxia
Nystagmus
Parkinson***
Extrapyramidal effects
Choreoathetosis

Eye Disorders

Diplopia
Blurred vision
Conjunctivitis

Gastrointestinal disorders

Vomiting
Gastrointestinal disturbance
Diarrhoea

Skin and subcutaneous tissue disorders

Skin rash**
Skin rash*

Musculoskeletal and connective tissue disorders

Unsteadiness

General disorders and administration site conditions

Tiredness
Headache
Drowsiness

*The rash, usually maculopapular in appearance, generally appears within eight weeks starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)
**serious skin rashes reported in SJS adults and children over 12 (see section 4.4)
***May worsen parkinsonia symptoms in patients with pre-existing Parkinsons disease

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported with out overt signs of hypersensitivity

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

Treatment
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
The pharmacotherapeutic group: Antiepileptics ATC-code: N03A X09

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

Pharmacodynamics
In tests designed to evaluate the central nervous system effects of 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.

5.2 Pharmacokinetic properties

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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline Cellulose
Cal carb 4450 PG (USP Calcium carbonate and NF Maltodextrin)
Cros piv o done
Povidone K-30
Aspartame
Low substituted hydrox ypropyl cellulose
Flavor mixed berries (Flavoring substance identical to natural substances (7.5%), Natural flavoring substances (0.0002%), Malodextrin (80.1%), E1518 Glycerol Triacetate (7.5 %))
Magnesium stearate
Colloidal anhydrous silica
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
White opaque HDPE bottles containing 28 or 30 tablets.
Polyamide/Aluminium/PVC/Aluminium foil blister packs containing 28 or 30 tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 20477/0011
PL 20477/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2007

10 DATE OF REVISION OF THE TEXT
02/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 5mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5mg lamotrigine.

Aspartame

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Dispensable tablets.

Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, debossed with ‘LII’ on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy: Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

4.2 Posology and method of administration
Administration
Lamotrigine tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

Dosage in monotherapy
Adults and children over 12 years (see Table 1)

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

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

Children aged 2 to 12 years
There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

Dosage in add-on therapy
Adults and children over 12 years (see Table 1)

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

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

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

Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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 (once a day)</td>
<td></td>
<td>50 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td><strong>Add-on therapy with valproate regardless of any concomitant medications</strong></td>
<td>12.5 mg (given 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
</tbody>
</table>

To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks.
Add-on therapy without valproate

<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>This dosage regimen should be used with: phenytoin carbamazepine phenobarbital primidone or with other inducers of lamotrigine glucuronidation (see section 4.5).</td>
<td>50 mg (once a day)</td>
<td>100 mg (two divided doses)</td>
<td>doses may be increased by 25 – 50 mg every one to two weeks</td>
</tr>
<tr>
<td></td>
<td>200 – 400 mg (two divided doses)</td>
<td>To achieve maintenance, doses may be increased by 100 mg every one to two weeks</td>
<td></td>
</tr>
</tbody>
</table>

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

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

Children aged 2 to 12 years

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

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

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

| Table 2 Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/day) |
| Treatment regimen                                                                 | Weeks 1 + 2          | Weeks 3 + 4          | Usual Maintenance Dose                               |
| Add-on therapy with valproate regardless of any other concomitant medication | 0.15 mg/kg* (once a day) | 0.3 mg/kg (once a day) | 0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses). |
| Add-on therapy without valproate                                                 | 0.6 mg/kg (two divided doses) | 1.2 mg/kg (two divided doses) | 1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses). |
or with other inducers of lamotrigine glucuronidation (see section 4.5).

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

* If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

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

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

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

**Women and Hormonal Contraceptives (see sections 4.4 and 4.5)**
(a) Starting lamotrigine in patients taking hormonal contraceptives
Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

(c) Stopping hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation the maintenance dose of lamotrigine may need to be decreased by as much as 50%, according to clinical response (see sections 4.4 and 4.5).

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

**Pregnancy and post-partum**
Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

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

**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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
• High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
• Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with Phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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>
<thead>
<tr>
<th>Table 3 Effects of other drugs on glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that significantly inhibit glucuronidation of lamotrigine</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
<tr>
<td>Phenytin</td>
</tr>
<tr>
<td>Primidone</td>
</tr>
<tr>
<td>Rifampicin</td>
</tr>
<tr>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

Interactions involving Oral Contraceptives

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during con-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

Effect of lamotrigine on oral contraceptives:

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

4.6 Pregnancy and lactation

Fertility

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

Teratogenicity

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (>1/100, <1/10), uncommon (>1/1,000, <1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
<td>Lupus</td>
<td></td>
<td>Stevens Johnson syndrome Lyell syndrome Hypersensitivity</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Aplastic anaemia agranulocytosis</td>
<td>Neutropenia Leucopenia Anaemia Thrombocytopenia Pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aggression Agitation Confusion and Hallucinations</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td></td>
<td></td>
<td>Increase in seizure</td>
<td>Dizziness Insomnia Tremor Tics</td>
<td></td>
</tr>
</tbody>
</table>
### Ataxia
- Nystagmus
- Parkinson***
- Extrapyramidal effects
- Choreaathetosis

### Eye Disorders
- Diplopia
- Blurred vision
- Conjunctivitis

### Gastrointestinal disorders
- Vomiting
- Gastrointestinal disturbance
- Diarrhoea

### Skin and subcutaneous tissue disorders
- Skin rash**

### Musculoskeletal and connective tissue disorders
- Unsteadiness

### General disorders and administration site conditions
- Tiredness
- Headache
- Drowsiness

---

*The rash, usually maculopapular in appearance, generally appears within eight weeks starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)*

**serious skin rashes reported in SJS adults and children over 12 (see section 4.4)**

***May worsen parkinsonia symptoms in patients with pre-existing Parkinsons disease***

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported with out overt signs of hypersensitivity

### 4.9 Overdose

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

#### Treatment
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
The pharmacotherapeutic group: Antiepileptics ATC-code: N03A X09

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

#### Pharmacodynamics
In tests designed to evaluate the central nervous system effects of 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.

5.2 Pharmacokinetic properties
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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline Cellulose
Cal carb 4450 PG (USP Calcium carbonate and NF Maltodextrin)
Crospovidone
Povidone K-30
Aspartame
Low substituted hydroxypropyl cellulose
Flavor mixed berries (Flavoring substance identical to natural substances (7.5%), Natural flavoring substances (0.0002%), Malodextrin (80.1%), E1518 Glyceryl Triacetate (7.5 %))
Magnesium stearate
Colloidal anhydrous silica
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Aluminium foil blister packs containing 28 or 30 tablets.
Polyamide/Aluminium/PVC/Aluminium foil blister packs containing 28 or 30 tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 20477/0012
PL 20477/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2007

10 DATE OF REVISION OF THE TEXT
02/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 25mg Dispersible Tablets

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

Aspartame

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Dispersible tablets.

Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, debossed with ‘LI2’ on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy: Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

4.2 Posology and method of administration
Adminstration
Lamotrigine tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

Dosage in monotherapy
Adults and children over 12 years (see Table 1)

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

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

Children aged 2 to 12 years
There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

Dosage in add-on therapy
Adults and children over 12 years (see Table 1)

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

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

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

Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>50 mg</td>
<td>To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
<tr>
<td></td>
<td>(once a day)</td>
<td>(once a day)</td>
<td></td>
</tr>
<tr>
<td><strong>Add-on therapy with valproate regardless of any concomitant medications</strong></td>
<td>12.5 mg</td>
<td>25 mg</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td>(given 25 mg on alternate days)</td>
<td>(once a day)</td>
<td>To achieve maintenance,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**UKPAR Lamotrigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets**

**Add-on therapy without valproate**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>50 mg (once a day)</td>
</tr>
<tr>
<td>100 mg</td>
<td>100 mg (two divided doses)</td>
</tr>
<tr>
<td>200 – 400 mg</td>
<td>200 – 400 mg (two divided doses)</td>
</tr>
</tbody>
</table>

**Note:** In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

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

**Children aged 2 to 12 years**

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

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

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

**Table 2 Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/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>Add-on therapy with valproate regardless of any other concomitant medication</td>
<td>0.15 mg/kg* (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses)</td>
</tr>
<tr>
<td>Add-on therapy without valproate</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses)</td>
</tr>
</tbody>
</table>
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see Section 4.4).

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

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

Women and Hormonal Contraceptives (see sections 4.4 and 4.5)
(a) Starting lamotrigine in patients taking hormonal contraceptives
Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

(c) Stopping hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation the maintenance dose of lamotrigine may need to be decreased by as much as 50%, according to clinical response (see sections 4.4 and 4.5).

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

Pregnancy and post-partum
Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

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

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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
• High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
• Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with Phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction
UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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 3 Effects of other drugs on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Drugs that significantly inhibit glucuronidation of lamotrigine</th>
<th>Drugs that significantly induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

Interactions involving Oral Contraceptives

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

Effect of lamotrigine on oral contraceptives:

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

4.6 Pregnancy and lactation

Fertility

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

Teratogenicity

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
<td>Lupus</td>
<td>Stevens Johnson syndrome Lyell syndrome Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Aplastic anaemia agranulocytosis</td>
<td>Neutropenia Leucopenia Anaemia Thrombocytopenia Pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Aggression Agitation Confusion and Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td></td>
<td></td>
<td>Increase in seizure</td>
<td>Dizziness Insomnia Tremor Tics</td>
<td></td>
</tr>
</tbody>
</table>
Ataxia  
Nystagmus  
Parkinson***  
Extrapyramidal effects  
Choreoathetosis  

Eye Disorders  
Diplopia  
Blurred vision  
Conjunctivitis  

Gastrointestinal disorders  
Vomiting  
Gastrointestinal disturbance  
Diarrhoea  

Skin and subcutaneous tissue disorders  
Skin rash**  
Skin rash*  

Musculoskeletal and connective tissue disorders  
Unsteadiness  

General disorders and administration site conditions  
Tiredness  
Headache  
Drowsiness  

*The rash, usually maculopapular in appearance, generally appears within eight weeks starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)  
**serious skin rashes reported in SJS adults and children over 12 (see section 4.4)  
***May worsen parkinsonia symptoms in patients with pre-existing Parkinsons disease

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported with out overt signs of hypersensitivity

4.9 Overdose  

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

Treatment  
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES  

5.1 Pharmacodynamic properties  
The pharmacotherapeutic group: Antiepileptics  
ATC-code: N03A X09

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

Pharmacodynamics  
In tests designed to evaluate the central nervous system effects of 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.

5.2 Pharmacokinetic properties

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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data
Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- Microcrystalline cellulose
- Crospovidone
- Calcium Carbonate 4450 (Constituents USP Calcium Carbonate and NF Maltodextrin)
- Aspartame (E951)
- Povidone K-30
- Low substituted hydroxypropyl cellulose
- Magnesium stearate
- Colloidal anhydrous silica
- Talc
- Mixed berry Flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Unit dose blister pack, which comprises of clear, transparent PVC film coated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons,
or
Cold form blister pack comprising of cold form blister laminate (having the following structure: oriented polyamide, aluminium foil, film polyvinyl chloride) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons.

PVC/PVdC Blister packs or polyamide / Aluminium / PVC / Aluminium foil blister containing 1,2,4,7,10,14,28,30, 56, 98 and 100 dispersible tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany
UKPAR Lamotrigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets  PL 20477/0011-15, 0020-22

8  MARKETING AUTHORISATION NUMBER(S)
   PL 20477/0013

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   02/03/2007

10 DATE OF REVISION OF THE TEXT
    02/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 50mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50mg lamotrigine.
Aspartame
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Dispersible tablets.
Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, debossed with ‘LI3’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Epilepsy: Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

4.2 Posology and method of administration
Administration
Lamotrigine tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

Dosage in monotherapy
Adults and children over 12 years (see Table 1)

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

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

Children aged 2 to 12 years
There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

Dosage in add-on therapy
Adults and children over 12 years (see Table 1)

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

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

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

Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
<tr>
<td>Add-on therapy with valproate regardless of any concomitant medications</td>
<td>12.5 mg (given 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance,</td>
</tr>
</tbody>
</table>
Add-on therapy without valproate

This dosage regimen should be used with:
- phenytoin
- carbamazepine
- phenobarbital
- primidone
- or with other inducers of lamotrigine glucuronidation (see section 4.5).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Usual Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (once a day)</td>
<td>0.15 mg/kg*</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses).</td>
</tr>
<tr>
<td>100 mg (two divided doses)</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses).</td>
</tr>
</tbody>
</table>

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

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

**Children aged 2 to 12 years**

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

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

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

**Table 2 Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/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>Add-on therapy with valproate regardless of any other concomitant medication</td>
<td>0.15 mg/kg* (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses).</td>
</tr>
<tr>
<td>Add-on therapy without valproate</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses).</td>
</tr>
</tbody>
</table>
or with other inducers of lamotrigine glucuronidation (see section 4.5).

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

* If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

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

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

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

Women and Hormonal Contraceptives (see sections 4.4 and 4.5)
(a) Starting lamotrigine in patients taking hormonal contraceptives
Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

(c) Stopping hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation the maintenance dose of lamotrigine may need to be decreased by as much as 50%, according to clinical response (see sections 4.4 and 4.5).

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

Pregnancy and post-partum
Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

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

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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
- High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
- Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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>
<thead>
<tr>
<th>Drugs that significantly inhibit glucuronidation of lamotrigine</th>
<th>Drugs that significantly induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

**Interactions involving Oral Contraceptives**

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

**Effect of lamotrigine on oral contraceptives:**

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

### 4.6 Pregnancy and lactation

**Fertility**

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

**Teratogenicity**

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
<td>Lupus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stevens Johnson syndrome</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lyell syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Aplastic anaemia agranulocytosis</td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leucopenia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anaemia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Aggression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Agitation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Confusion and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td></td>
<td></td>
<td>Increase in seizure</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tics</td>
<td></td>
</tr>
</tbody>
</table>
### 4.9 Overdose

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

**Treatment**
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

---

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

The pharmacotherapeutic group: Antiepileptics  ATC-code: N03A X09

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

**Pharmacodynamics**
In tests designed to evaluate the central nervous system effects of 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

<table>
<thead>
<tr>
<th>Eye Disorders</th>
<th>Ataxia Nystagmus Parkinson*** Extrapyramidal effects Choreoathetosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting Gastrointestinal disturbance Diarrhoea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin rash**</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Unsteadiness</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Tiredness Headache Drowsiness</td>
</tr>
</tbody>
</table>

*The rash, usually maculopapular in appearance, generally appears within eight weeks starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)
**serious skin rashes reported in SJS adults and children over 12 (see section 4.4)
***May worsen parkinsonia symptoms in patients with pre-existing Parkinsons disease

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported with out overt signs of hypersensitivity
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.

5.2 Pharmacokinetic properties

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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Crospovidone
Cal Carb 4450 (Constituents USP Calcium Carbonate and NF Maltodextrin)
Aspartame (E951)
Povidone K-30
Low substituted hydroxypropyl cellulose
Magnesium stearate
Colloidal anhydrous silica
Talc
Mixed berry flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Unit dose blister pack, which comprises of clear, transparent PVC film coated with PVDc on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons, or

Cold form blister pack comprising of cold form blister laminate (having the following structure: oriented polyamide, aluminium foil, film polyvinyl chloride) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons.

PVC/PVDc Blister packs or polyamide/Aluminium / PVC/Aluminium foil blister containing 1,2,4,7,10,14,28,30,56,98 and 100 dispersible tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany
UKPAR Lamotrigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets

8 MARKETING AUTHORISATION NUMBER(S)
   PL 20477/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   02/03/2007

10 DATE OF REVISION OF THE TEXT
    02/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Lamotrigine 100mg Dispersible Tablets

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

Aspartame

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Dispersible tablets.

Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, deossed with ‘LI4’ on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Epilepsy: Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

4.2 Posology and method of administration

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

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

Dosage in monotherapy

Adults and children over 12 years (see Table 1)

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

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

Children aged 2 to 12 years

There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

Dosage in add-on therapy

Adults and children over 12 years (see Table 1)

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

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

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

Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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</td>
<td>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
<tr>
<td>Add-on therapy with valproate regardless of any concomitant medications</td>
<td>12.5 mg (given 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance,</td>
</tr>
</tbody>
</table>
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see Section 4.4).

Children aged 2 to 12 years

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

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

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

Table 2 Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/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>Add-on therapy with valproate regardless of any other concomitant medication</td>
<td>0.15 mg/kg* (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses).</td>
</tr>
<tr>
<td>Add-on therapy without valproate</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses).</td>
</tr>
</tbody>
</table>
or with other inducers of lamotrigine glucuronidation (see section 4.5).

<table>
<thead>
<tr>
<th>doses</th>
<th>doses</th>
<th>doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>or with other inducers of lamotrigine glucuronidation (see section 4.5).</td>
<td>or with other inducers of lamotrigine glucuronidation (see section 4.5).</td>
<td>or with other inducers of lamotrigine glucuronidation (see section 4.5).</td>
</tr>
</tbody>
</table>

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

* If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.

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

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

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

**Women and Hormonal Contraceptives (see sections 4.4 and 4.5)**
(a) Starting lamotrigine in patients taking hormonal contraceptives
Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

(c) Stopping hormonal contraceptives in patients taking lamotrigine
For women NOT taking inducers of lamotrigine glucuronidation the maintenance dose of lamotrigine may need to be decreased by as much as 50%, according to clinical response (see sections 4.4 and 4.5).

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

**Pregnancy and post-partum**
Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

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

**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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
- High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
- Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with Phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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 3 Effects of other drugs on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Drugs that significantly inhibit glucuronidation of lamotrigine</th>
<th>Drugs that significantly induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenotoin</td>
</tr>
<tr>
<td></td>
<td>Primidone</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

Interactions involving Oral Contraceptives

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

Effect of lamotrigine on oral contraceptives:

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

4.6 Pregnancy and lactation

Fertility

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

Teratogenicity

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
<td></td>
<td>Lupus</td>
<td>Stevens Johnson syndrome Lyell syndrome Hypersensitivity</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Aplastic anaemia agranulocytosis</td>
<td>Neutropenia Leucopenia Anaemia Thrombocytopenia Pancytopenia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aggression Agitation Confusion and Hallucinations</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td></td>
<td></td>
<td></td>
<td>Increase in seizure</td>
<td>Dizziness Insomnia Tremor Tics</td>
</tr>
</tbody>
</table>
Ataxia
Nystagmus
Parkinson***
Extrapyramidal
effects
Choreoathetosis

Eye Disorders
Diplopia
Blurred vision
Conjunctivitis

Gastrointestinal
disorders
Vomiting
Gastrointestinal
disturbance
Diarrhoea

Skin and
subcutaneous
tissue disorders
Skin rash**
Skin rash*

Musculoskeletal
and connective
tissue disorders
Unsteadiness

General
disorders and
administration
site conditions
Tiredness
Headache
Drowsiness

*The rash, usually maculopapular in appearance, generally appears within eight weeks
starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)
**serious skin rashes reported in SJS adults and children over 12 (see section 4.4)
***May worsen parkinsonia symptoms in patients with pre-existing Parkinsons disease

Elevations of liver function tests and rare reports of hepatic dysfunction, including
hepatic failure, have been reported. Hepatic dysfunction usually occurs in association
with hypersensitivity reactions but isolated cases have been reported with out overt
signs of hypersensitivity

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

Treatment
In the event of overdosage, the patient should be admitted to hospital and given appropriate
supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
The pharmacotherapeutic group: Antiepileptics ATC-code: N03A X09

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

Pharmacodynamics
In tests designed to evaluate the central nervous system effects of 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.

5.2 Pharmacokinetic properties

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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Crospovidone
Cal Carb 4450 (Constituents USP Calcium Carbonate and NF Maltodextrin)
Aspartame (E951)
Povidone K-30
Low substituted hydroxypropyl cellulose
Magnesium stearate
Colloidal anhydrous silica
Talc
Mixed berry flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Unit dose blister pack, which comprises of clear, transparent PVC film coated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons,
or
Cold form blister pack comprising of cold form blister laminate (having the following structure: oriented polyamide, aluminium foil, film polyvinyl chloride) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons.

PVC/PVdC Blister packs or polyamide /Aluminium / PVC /Aluminium foil blister containing 1,2,4,7,10,14,28,30, 56, 98 and 100 dispersible tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany
MARKETING AUTHORISATION NUMBER(S)
PL 20477/0015

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2007

DATE OF REVISION OF THE TEXT
02/03/2007
NAME OF THE MEDICINAL PRODUCT
Lamotrigine 200mg Dispersible Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg lamotrigine.

Aspartame

For full list of excipients, see section 6.1

PHARMACEUTICAL FORM
Dispersible tablets.

Lamotrigine tablets are white to off-white, uncoated, circular, flat-bevelled tablets, debossed with ‘LI5’ on one side and plain on the other side.

CLINICAL PARTICULARS

Therapeutic indications
Epilepsy: Monotherapy in adults and children over 12 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures

Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Add-on therapy in adults and children over 2 years of age:
Simple partial seizures
Complex partial seizures
Secondarily generalised tonic-clonic seizures
Primary generalised tonic-clonic seizures
Lamotrigine Tablets are also indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome.

Posology and method of administration
Administration
Lamotrigine tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

If a calculated dose of lamotrigine (e.g. for use in children and 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.

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (AEDs) are added-on to treatment regimes containing Lamotrigine consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 Interaction with other Medicinal Products and other Forms of Interaction).

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, as though initiating therapy (see section 4.2).

**Dosage in monotherapy**

**Adults and children over 12 years (see Table 1)**

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

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

**Children aged 2 to 12 years**

There is insufficient evidence available from appropriate studies in children, upon which to base dosage recommendations for monotherapy use in children under the age of 12 years (see Section 4.1).

**Dosage in add-on therapy**

**Adults and children over 12 years (see Table 1)**

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

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

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

### Table 1 Recommended treatment regimen for adults and children over 12 years of age

<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>25 mg (once a day)</td>
<td>50 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks</td>
</tr>
<tr>
<td><strong>Add-on therapy with valproate regardless of any concomitant medications</strong></td>
<td>12.5 mg (given 25 mg on alternate days)</td>
<td>25 mg (once a day)</td>
<td>100 – 200 mg (once a day or two divided doses) To achieve maintenance,</td>
</tr>
</tbody>
</table>


doses may be increased by 25 – 50 mg every one to two weeks

Add-on therapy
without valproate

This dosage regimen should be used with:
phenytoin
carbamazepine
phenobarbital
primidone
or with other inducers of lamotrigine glucuronidation (see section 4.5).

50 mg
(once a day)

100 mg
(two divided doses)

200 – 400 mg
(two divided doses)

To achieve maintenance, doses may be increased by 100 mg every one to two weeks

Note: In patients taking AEDs 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, thereafter, the dose should be increased until optimal response is achieved.

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

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

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

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

Table 2 Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/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>Add-on therapy with valproate regardless of any other concomitant medication</td>
<td>0.15 mg/kg* (once a day)</td>
<td>0.3 mg/kg (once a day)</td>
<td>0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses).</td>
</tr>
<tr>
<td>Add-on therapy without valproate</td>
<td>0.6 mg/kg (two divided doses)</td>
<td>1.2 mg/kg (two divided doses)</td>
<td>1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided</td>
</tr>
</tbody>
</table>
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see Section 4.4).

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

**Children aged less than 2 years**

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

**Women and Hormonal Contraceptives (see sections 4.4 and 4.5)**

(a) Starting lamotrigine in patients taking hormonal contraceptives

Dose escalation should follow the guidelines recommended in Table 1 above (see sections 4.4 and 4.5).

(b) Starting hormonal contraceptives in patients taking lamotrigine

For women NOT taking inducers of lamotrigine glucuronidation such as phenytoin, carbamazepine, phenobarbital, primidone or rifampicin, the maintenance dose of lamotrigine may need to be increased by as much as two-fold, according to clinical response (see sections 4.4 and 4.5). For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

(c) Stopping hormonal contraceptives in patients taking lamotrigine

For women NOT taking inducers of lamotrigine glucuronidation the maintenance dose of lamotrigine may need to be decreased by as much as 50%, according to clinical response (see sections 4.4 and 4.5).

For women taking lamotrigine in addition to inducers of lamotrigine glucuronidation, adjustment may not be necessary.

**Pregnancy and post-partum**

Dose adjustment may be necessary during pregnancy and post-partum (see section 4.6).

**Elderly**

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

**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.
4.3 Contraindications
Lamotrigine Tablets are contraindicated in individuals with known hypersensitivity to lamotrigine.

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

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

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

Additionally the overall risk of rash appears to be strongly associated with:-
- High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see Section 4.2).
- Concomitant use of valproate (See Section 4.2).

All patients (adults and children) who develop a rash should be promptly evaluated and lamotrigine withdrawn immediately unless the rash is clearly not drug related. Lamotrigine should not be restarted in patients with previous hypersensitivity (see Section 4.3).

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

Specialist contraceptive advice should be given to women who are of child-bearing age. Women of child-bearing age should be encouraged to use effective alternative non-hormonal methods of contraception.

Effects of hormonal contraceptives on lamotrigine efficacy:
Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control in women on a stable lamotrigine dose who start an oral contraceptive, or in adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see sections 4.2 and 4.5).

The effects of co-administration of other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:
An interaction study demonstrated some loss of suppression of the hypothalamic-pituitary-ovarian axis when 300mg lamotrigine was co-administered with a combined oral contraceptive (see section 4.5). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy cannot be excluded. Therefore, women should have a review of their contraception when starting lamotrigine, and the use of alternative non-hormonal methods of contraception should be encouraged. A
hormonal contraceptive should only be used as the sole method of contraception if there is no other alternative. If the oral contraceptive pill is chosen as the sole method of contraception, women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g. breakthrough bleeding) while taking Lamotrigine as this may be an indication of decreased contraceptive efficacy. Women taking Lamotrigine should notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations.

As with other AEDs, abrupt withdrawal of Lamotrigine Tablets may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of Lamotrigine Tablets should be gradually decreased over a period of 2 weeks.

During clinical experience with lamotrigine used as add-on therapy, there have been, rarely, deaths following rapidly progressive illnesses with status epilepticus, rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation (DIC). The contribution of lamotrigine to these events remains to be established.

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

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.

In patients with severe hepatic impairment (Child-Pugh grade C) it has been shown that initial and maintenance doses should be reduced by 75%. Caution should be exercised when dosing this severely hepatically impaired population.

These tablets contain aspartame, which is a source of phenylalanine. This may be harmful for patients with Phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes, and interactions between lamotrigine and drugs 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 3 Effects of other drugs on glucuronidation of lamotrigine

<table>
<thead>
<tr>
<th>Drugs that significantly inhibit glucuronidation of lamotrigine</th>
<th>Drugs that significantly induce glucuronidation of lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Primidone</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Ethinylestradiol/ levonorgestrel combination*</td>
<td></td>
</tr>
</tbody>
</table>

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.
Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements.

Sodium valproate, which competes with lamotrigine for hepatic drug-metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold.

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

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

Interactions involving Oral Contraceptives

Effect of oral contraceptives on lamotrigine:

Systemic lamotrigine concentrations are approximately halved during co-administration of oral contraceptives. This may result in reduced seizure control after the addition of an oral contraceptive, or adverse effects following withdrawal of an oral contraceptive. Dose adjustments of lamotrigine may be required (see section 4.2).

In a study of 16 female volunteers, 30 mcg ethinylestradiol/150 mcg 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 gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

The effect of other hormonal contraceptive products or hormone replacement therapy has not been evaluated although the effect may be similar.

Effect of lamotrigine on oral contraceptives:

Co-administration of 300mg lamotrigine in a study of 16 female volunteers had no effect on the pharmacokinetics of the ethinylestradiol 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 follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol during the study indicated some loss of suppression of ovarian hormonal activity, 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

4.6 Pregnancy and lactation

Fertility

Administration of Lamotrigine Tablets did not impair fertility in animal reproductive studies.

There is no experience of the effect of Lamotrigine Tablets on human fertility.

Teratogenicity

Lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy. However, reproductive toxicology studies with Lamotrigine in animals at doses in excess of the human therapeutic dosage showed no teratogenic effects.
Pregnancy
There is insufficient data available on the use of Lamotrigine in human pregnancy to evaluate its safety. Lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Physiological changes during pregnancy may result in decreased lamotrigine levels. These changes in lamotrigine levels can occur from early in pregnancy and progress during pregnancy, then revert quickly after delivery. The dose of lamotrigine should not be increased routinely in pregnancy but should only be adjusted on clinical grounds. To maintain seizure control during pregnancy a dose increase may be needed, although other factors including vomiting should also be considered if seizure control deteriorates. Post-partum a dose decrease may be needed to avoid toxicity. Women on lamotrigine must be monitored closely during pregnancy and post-partum.

Lactation
There is limited information on the use of lamotrigine in lactation. Preliminary data indicates that it passes into breast milk in concentrations usually of the order of 40-60% of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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

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

4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Frequency not advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td></td>
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<td></td>
<td>Lupus</td>
<td>Stevens Johnson syndrome</td>
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<td>Lyell syndrome</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
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<td>Blood and lymphatic system disorders</td>
<td></td>
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<td>Aplastic</td>
<td>Neutropenia</td>
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<td></td>
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<td></td>
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<td>anaemia</td>
<td>Leucopenia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>agranulocytosis</td>
<td>Anaemia</td>
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<td></td>
<td>Thrombocytopenia</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Pancytopenia</td>
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<tr>
<td>Psychiatric disorders</td>
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<td>Aggression</td>
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<td>Agitation</td>
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<td></td>
<td>Confusion and Hallucinations</td>
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<td>Nervous system disorder</td>
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<td>Increase in seizure</td>
<td>Dizziness</td>
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<td>Insomnia</td>
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<td>Tremor</td>
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<td>Tics</td>
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</tbody>
</table>
| Eye Disorders | Ataxia  
Nystagmus  
Parkinson***  
Extrapyramidal effects  
Choreoathetosis | Diplopia   
Blurred vision   
Conjunctivitis |
|---------------|-------------------------------------------------------|
| Gastrointestinal disorders | Vomiting   
Gastrointestinal disturbance   
Diarrhoea |
| Skin disorders and subcutaneous tissue disorders | Skin rash**   
Skin rash* |
| Musculoskeletal and connective tissue disorders | Unsteadiness |
| General disorders and administration site conditions | Tiredness   
Headache   
Drowsiness |

*The rash, usually maculopapular in appearance, generally appears within eight weeks starting treatment and resolves on withdrawal of lamotrigine (see section 4.4)

**Serious skin rashes reported in SJS adults and children over 12 (see section 4.4)

***May worsen parkinsonia symptoms in patients with pre-existing Parkinson's disease

Elevations of liver function tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported with out overt signs of hypersensitivity

4.9 Overdose

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

Treatment
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
The pharmacotherapeutic group: Antiepileptics ATC-code: N03A X09

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

Pharmacodynamics
In tests designed to evaluate the central nervous system effects of 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.

5.2 Pharmacokinetic properties

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. The pharmacokinetics are linear up to 450mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations vary very little.

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.

The mean steady state clearance in healthy adults is 39 ± 14 ml/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

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

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

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 Section 4.2).

The results of pharmacokinetic studies of lamotrigine in 12 healthy elderly volunteers aged 65 to 76 years and 12 young volunteers aged 26 to 38 years following a 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg. A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

There is no experience of treatment with lamotrigine of patients with renal failure. Pharmacokinetic studies using single doses in subjects with renal failure indicate that lamotrigine pharmacokinetics are little affected but plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 ml/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 ml/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment (see Section 4.2).

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests indicate that Lamotrigine Tablets do not present a genetic risk to man.

Carcinogenicity
Lamotrigine Tablets were not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose
Crospovidone
Cal Carb 4450 (Constituents USP Calcium Carbonate and NF Maltodextrin)
Aspartame (E951)
Povidone K-30
Low substituted hydroxypropyl cellulose
Magnesium stearate
Colloidal anhydrous silica
Talc
Mixed berry flavour

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Unit dose blister pack, which comprises of clear, transparent PVC film coated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons, or Cold form blister pack comprising of cold form blister laminate (having the following structure: oriented polyamide, aluminium foil, film polyvinyl chloride) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Packed in cardboard cartons.

PVC/PVdC Blister packs or polyamide /Aluminium / PVC /Aluminium foil blister containing 1,2,4,7,10,14,28,30, 56, 98 and 100 dispersible tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Kohne Pharma GmbH
Schallbruch 1
D-42781 Haan
Germany
MARKETING AUTHORISATION NUMBER(S)
PL 20477/0020

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2007

DATE OF REVISION OF THE TEXT
02/03/2007
**UKPAR Lamotrigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets PL 20477/0011-15, 0020-22**

**PROMINENT INFORMATION LEAFLET**

**LAMOTRIGINE 2 mg DISPERSCIBLE TABLETS**

**Read all of this leaflet carefully before you start taking this medicine or give this medicine to your child. 
Keep this leaflet. You may need to read it again. 
If you have further questions, please ask your doctor or other healthcare professional.**

- **Lamotrigine Tablets contains 2 mg lamotrigine. 
- Lamotrigine Tablets are available as either 2 mg or 5 mg tablets. 
- Each dispersible tablet contains 2 mg lamotrigine.**

**WHAT LAMOTRIGINE TABLETS ARE AND WHAT THEY ARE USED FOR**

Lamotrigine belongs to a group of medicines called anticonvulsant medicines, used for treating epilepsy.

Each dispersible tablet contains 2 mg lamotrigine. The tablets are white in soft-safe, uncoated, circular, film-coated tablets which are debossed with ‘L’ on one side and plain on the other.

Lamotrigine is available as blisters or blister packs of 28 or 30 tablets. Not all pack sizes may be marketed.

Lamotrigine is used in the treatment of partial seizures (focal seizures) and generalized tonic-clonic seizures (grand mal seizures) associated with Lennox-Gastaut Syndrome in adults and children aged 12 years and over. Lamotrigine tablets may be used in children aged 2 to 12 years, lamotrigine is recommended only in children aged 2 to 12 years.

2 mg Lamotrigine Tablets are used in children aged 2 to 12 years. Usually Lamotrigine Tablets are used when starting treatment. The recommended daily dose of Lamotrigine Tablets would depend on the child’s weight and any other anticonvulsant medicines being taken simultaneously. 

2 mg and 5 mg Lamotrigine Tablets are used when starting treatment. The effective dose of Lamotrigine Tablets can be given in two divided daily doses. To ensure that the correct dose is given, your child’s weight must be measured and the dose reviewed as weight changes occur. 

The doctor may advice you to give Lamotrigine every day if your child’s weight doesn’t change as less as 1 to 2 mg/lb/day of lamotrigine. 

Doses less than 1 mg of lamotrigine are not recommended.

Take special care not to exceed the usual recommended daily doses. Do not exceed the recommended doses.

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

For adults and children over 12 years of age.

Lamotrigine use alone or as a single antiepileptic medication. 
Your doctor would start your treatment with 25 mg of lamotrigine taken once a day for the first 2 weeks, followed by 50 mg of lamotrigine taken once a day during the 3rd and 4th weeks. Therefore, your doctor may increase your dose over the next few weeks depending on your response to the treatment. Most patients would require a dose of 100-200 mg, 500-1000 mg taken once a day or in two divided doses.

Lamotrigine is used alone and also for the treatment of children and adults under the age of 12 years.

3. Lamotrigine can cause nausea, vomiting, hyperactivity, irritability, restlessness, or could cause the feeling of a foreign individual.

4. Possible Side Effects

Side effects can cause nausea, vomiting, hyperactivity, irritability, restlessness, or could cause the feeling of a foreign individual.

These are all of very serious side effects, if you or your child experiences these, you or your child may have suffered a serious allergic reaction to lamotrigine. You need to call emergency services.

5. Further Information

Other antiepileptic medicines have been used with lamotrigine, and it has not been found that lamotrigine affects the other antiepileptic medicines.

6. Storage and Disposal

Take this medicine as instructed by your doctor. Check the label carefully for how much and how often to take this medicine. Your pharmacist or doctor can help you to take your medicine correctly. 

Please note that the recommended daily doses are based on previous clinical trial data. Your doctor may give you instructions which may be different from those given below especially if your child has been prescribed lamotrigine for preventing seizures.

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

**HOW TO TAKE LAMOTRIGINE TABLETS**

This medicine must be taken with food. 
- If you have further questions, please ask your doctor or pharmacist. 
- If you have any concerns, please ask for more information.

**DO NOT TAKE LAMOTRIGINE IF**

- You or your child have previously had an allergic reaction to lamotrigine or to any of the ingredients listed above, (allergic reaction may include rash, itching, swelling, wheezing, shock, or anaphylaxis, or bronchospasm or difficulty breathing). 
- You or your child have certain medical conditions or taking other medicines, or are pregnant or breast-feeding.

**DO NOT TAKE LAMOTRIGINE IF**

- You or your child have certain medical conditions or taking other medicines, or are pregnant or breast-feeding.

**DO NOT TAKE LAMOTRIGINE IF**

- You or your child have certain medical conditions or taking other medicines, or are pregnant or breast-feeding.

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- You or your child have certain medical conditions or taking other medicines, or are pregnant or breast-feeding.

This leaflet was prepared on 23 December 2015.
PATIENT INFORMATION LEAFLET

LAMOTRIGINE 5 mg DISPERSIBLE TABLETS

5. Storing Lamotrigine Tablets

Store in the original package. Keep container tightly closed. Keep out of the reach of children.

If you do not take the tablets from the blister pack, please take them back to the pharmacist.

This leaflet was prepared on 23 November 2005.

UKPAR Lamotrigine 2.5, 25, 50, 100, 200, 2022-003
UKPAR Lamotrigine 2, 5, 25, 50, 100, 200mg Dispersible Tablets PL 20477/0011-15, 0020-22

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

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

1. What Lamotrigine Dispersible Tablets are and what they are used for

2. Before you take Lamotrigine Dispersible Tablets

3. How to take Lamotrigine Dispersible Tablets

4. Possible Side Effects

5. Storing Lamotrigine Dispersible Tablets

The name of your medicine is Lamotrigine 25mg Dispersible Tablets or Lamotrigine 50mg Dispersible Tablets or Lamotrigine 100mg Dispersible Tablets or Lamotrigine 200mg Dispersible Tablets, but will be referred to as Lamotrigine Dispersible Tablets throughout this Patient Information Leaflet.

Each dispersible tablet contains 25 mg, 50 mg, 100 mg or 200 mg of Lamotrigine. The active ingredient is lamotrigine.

Other ingredients are microcrystalline cellulose, carm 4450PG, povidone K30, flavour mixture, aspartame (E951), low substituted hydroxypropyl cellulose, talc, colloidal anhydrous silica, magnesium stearate.

Marketing Authorisation Holder: Kohn Pharma GmbH, Schalbruch 1, D-42781 Hoern, Germany.

Manufacturer: Ranbaxy Ireland Limited, Spatfield, Cork Road, Cashel, Co Tipperary, Republic of Ireland and Basics GmbH, 261 Hammelrath Weg, Baggaciz G1, Lerkusen 51377, Germany.

1. What Lamotrigine Dispersible Tablets are and what they are used for

Lamotrigine Dispersible Tablets come in 4 strengths. All tablets are white to off white round tablets with a slightly waxy finish. Each strength has a different marking printed on it to help you identify it:

25mg: Printed with ‘L2’ on one side and plain on the other.
50mg: Printed with ‘L2’ on one side and plain on the other.
100mg: Printed with ‘L14’ on one side and plain on the other.
200mg: Printed with ‘L5’ on one side and plain on the other.

Lamotrigine Dispersible Tablets are available in blister packs containing 1, 2, 4, 7, 10, 14, 28, 30, 60, 98 or 100 dispersible tablets. Not all pack sizes may be marketed.

Lamotrigine Dispersible Tablets are one of a group of medicines called anticonvulsants which are used to treat various types of epilepsy in adults and children. The tablets may be used on their own to treat adults and children over 12 years of age. They can also be used in combination with other antiepileptic medicines in both adults and children aged 2 years and over.

2. Before you take Lamotrigine Dispersible Tablets

This medicine suits most people, but there are a few who should not take it, or who need to ask their doctor before doing so. You can answer yes to any of the questions below (or if you are unsure that they apply) and these points have not already been discussed with your doctor, tell your doctor or pharmacist before taking these tablets:

• Are you pregnant, trying to become pregnant or breast-feeding?
• Have you previously had an allergic reaction to lamotrigine or to any of the other ingredients in Lamotrigine Dispersible Tablets?
• Are you taking any other medicines?
• Are you taking oral contraceptive pills?
• Do you have liver or kidney disease?
• Do you suffer from Parkinson’s disease?
• Are you taking any other medicine to treat epilepsy (for example phenytoin, carbamazepine, phenobarbital or primidone)?

Important information about some of the ingredients of Lamotrigine Dispersible Tablets:

These tablets contain small amounts of Aspartame (E951). Aspartame contains a source of phenylalanine, which may be harmful for people with Phenylketonuria.

Taking Lamotrigine Tablets and the Contraceptive Pill

If you are a woman who is already using a hormonal contraceptive method known as the ‘pill’ and intend to start treatment with lamotrigine, the method of contraception you use should be reviewed by your doctor. Other non-hormonal methods of contraception should be used. The pill should be used as the only method of contraception if there is no other alternative.

If you are a woman who is already taking lamotrigine and intend to start or stop using a hormonal contraceptive known as the ‘pill’, you should discuss this with your doctor who may need to change your dose of lamotrigine. Lamotrigine may reduce the effectiveness of the contraceptive pill. Contact your doctor as soon as possible if you notice any changes in your menstrual patterns (e.g. break-through bleeding or spotting) as this may be a sign of reduced effectiveness of the contraceptive pill. Remember that changes in your menstrual cycle patterns may not always occur even if the effectiveness of the contraceptive pill is reduced.

3. How to take Lamotrigine Dispersible Tablets

Your doctor will tell you when and how to take your medicine. Please note: your doctor may give you different instructions to those written below. It is important to take your medicine in the way your doctor has told you to, if you are unsure always check with your doctor. The dose your doctor will prescribe for you depends on whether you are taking other anti-epileptic medicines and so which one(s). This is especially important if you are taking any medicine containing vitamin B6. The pharmacist’s label on your pack will tell you how many tablets to take and how often to take them. If the label doesn’t say, or if you are not sure, ask your doctor or pharmacist.

Adults and children over 12 years old:
The usual dose used to control epilepsy is between 100 mg and 400 mg, taken once daily or divided into two equal doses each day. When you first start taking Lamotrigine Dispersible Tablets, your doctor will prescribe a much lower dose than this and will then increase your dose gradually over a few weeks.

Children between 2 and 12 years of age:
The usual dose used to control epilepsy is between 1 mg and 15 mg per kilogram of your child’s body weight, taken once daily or divided into two equal doses each day. When your child first starts taking Lamotrigine Dispersible Tablets, your doctor will prescribe a much lower dose than this for your child and will then increase it gradually over a few weeks.

Lamotrigine Dispersible Tablets are not recommended for use in children under 2 years of age.

The 25 mg dispersible tablet is currently the lowest strength available if the required dose is less than 12.5 mg. Lamotrigine Dispersible Tablets should not be administered.

If your child has liver disease your doctor may prescribe less than the recommended dose, depending on how severe the liver condition is.

A tablet can be swalloed whole with a little water, chewed or can be dissolved in water to make a liquid medicine:

• If the tablet is chewed, you need to drink a little water at the same time. This is because the tablet needs water dissolving in the mouth. Then sip a little more water to make sure all of the medicine has been taken.
• To make a liquid medicine, add the tablet to a little water in a glass. Use enough water to cover the whole tablet. Leave for about 1 minute, until the tablet has fully dissolved, and then drink all of the liquid. Add a little more water to the glass and drink this to make sure all of the medicine has been taken.

If you take too many tablets:

Do not take more tablets in one day than your doctor tells you to. If you take too many Lamotrigine Dispersible Tablets, or if someone else takes your medicine by mistake, contact your doctor or nearest casualty department immediately, taking this leaflet or some text with you so the doctor will know what you have taken.

If you forget to take Lamotrigine Dispersible Tablets:

If you forget to take a dose as soon as you remember and then go on as you should. Do not take a double dose to make up.

Do not stop taking your medicine suddenly. Ask your doctor first.

4. Possible Side Effects

Like all medicines, Lamotrigine Dispersible Tablets can cause side effects. However, most people taking this medicine find that it causes no problems.

If you experience any of the symptoms described below it is important to tell your doctor IMMEDIATELY as more serious problems may develop if left ignored. Some of these reactions are known to be more common in children, so parents should be especially aware of this:

- Unexpected skin rash for example a rash and/or a sore mouth or eyes
- Swelling around the face
- High temperature, ‘flu-like’ symptoms, swollen glands or diarrhoea or if your child gets worse during your first month of treatment with Lamotrigine Dispersible Tablets
- If you start to get lots of infections (for example a cold) with a sore throat or mouth ulcer
- If you begin to feel very tired or if you develop any unexpected bruising or blisters

If you experience any of the symptoms described below it is important to tell your doctor as soon as possible:

- Blurred vision, redness of the eye (conjunctivitis), dizziness, headache, difficulty sleeping
- Feeling hot or being sick, diarrhoea, hallucinations, feeling irritable, aggressive, agitation or confusion
- Unsteadiness or loss of co-ordination when you walk
- If you have Parkinson’s disease, any worsening of your symptoms such as shaking of the arms or legs, rolling of the eyes or a slowing movement of the mouth
- Unusual movements that you can’t control such as irregular jerking or shaking of the arms or legs
- If your seizures become more frequent

Very rarely, abnormalities in liver function may occur. If you have one or more of the following symptoms, which may or may not be accompanied by feeling sick and generally unwell, tell your doctor immediately:

- Yellowing of the skin
- itching
- Abdominal pain and/or tenderness.

Tell your doctor or pharmacist if you notice any other side effects from your medicine, which is not mentioned here.

5. Storing Lamotrigine Dispersible Tablets

Do not use these tablets after their expiry date which is printed on the packaging. If the tablets are out of date, return them to your pharmacist and, if necessary, get a new prescription from your doctor.

Do not store above 25°C. Store in the original packaging. Keep in a safe place out of the reach and sight of children. If your doctor decides to stop treatment for you or your child with Lamotrigine Dispersible Tablets, return any remaining tablets to a pharmacist.

REMEMBER these tablets have been prescribed for you or your child. NEVER give them to anyone else. The tablets may harm them, even if their symptoms are the same as yours.

If you have any questions about your treatment which are not answered in this leaflet, speak with your doctor or pharmacist for more information.

This leaflet applies only to Lamotrigine Dispersible Tablets and was prepared in March 2008.

87
Each dispersible tablet contains 2 mg of lamotrigine. The tablets also contain aspartame. For oral use only. These tablets may be chewed, dispersed in water or swallowed whole.

Use as directed by a physician. Do not exceed the stated dose. Store in the original package.
Each dispersible tablet contains 5 mg of lamotrigine. The tablets also contain aspartame. For oral use only. These tablets may be chewed, dispersed in water or swallowed whole.

Use as directed by a physician. Do not exceed the stated dose. Store in the original package.
PACKAGING – Lamotrigine 100mg Dispersible Tablets (PL 20477/0015)
### PACKAGING – Lamotrigine 2mg Dispersible Tablets (PL 20477/0021)

<table>
<thead>
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<th>Lamotrigine 2mg Dispersible Tablets</th>
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<td><strong>RANBAXY</strong></td>
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<td>Kohne Pharma GmbH</td>
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Each dispersible tablet contains 2mg of lamotrigine.

The tablets also contain aspartame.

For oral use only. These tablets may be chewed, dispersed in water or swallowed whole.

Use as directed by a physician.

Do not exceed the stated dose.

Store in the original package.

MA Holder: Kohne Pharma GmbH
Schwalbruch 1, D-42761 Haan Germany

PL No. 20477/0021

Distributor: Ranbaxy (UK) Limited
95 Park Lane, Mayfair, London W1K 7JE UK
Each dispersible tablet contains 2 mg of lamotrigine.
The tablets also contain aspartame.
For oral use only. These tablets may be chewed, dispersed in water or swallowed whole.

Use as directed by a physician.
Do not exceed the stated dose.
Store in the original package.

MA Holder:
Koeln Pharma GmbH
Schaifbruch 1, D-42781 Haan
Germany
PL No. 20477/0021

Distributor:
Ranbaxy (UK) Limited
96 Park Lane, Mayfair,
London W1K 7TE
UK
PACKAGING – Lamotrigine 5mg Dispersible Tablets (PL 20477/0022)

Each dispersible tablet contains 5 mg of lamotrigine.
The tablets also contain aspartame.
For oral use only. These tablets may be chewed, dispersed in water or swallowed whole.

Use as directed by a physician.
Do not exceed the stated dose.
Store in the original package.

MA Holder: Kohne Pharma GmbH
Schallbruch 1, D-42781 Hagen, Germany
PL No: 20477/0022

Distributor: Ranbaxy (UK) Limited
95 Pink Lane, Myfair, London W1K 7LE, UK

Size: 116
Market: U
Proof: 5-1