Public Assessment Report

Mutual Recognition Procedure

Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Dispersible Tablets

UK/H/822/01-06

UK licence no: PL 20137/0022-7

Clarendon Pharma Limited
LAY SUMMARY

The MHRA has granted Clarendon Pharma Limited Marketing Authorisations (licenses) for the medicinal products Lamotrigine 2mg, 5mg, 25mg, 50mg 100mg and 200mg Dispersible Tablets (PL 20137/0022-7).

These are prescription only medicines (POM) for the treatment of different forms of epilepsy.

Lamotrigine 2mg, 5mg, 25mg, 50mg 100mg and 200mg Dispersible Tablets contain the active ingredient lamotrigine. Lamotrigine is thought to be able to block the amino acid that plays a key role in the generation of epileptic seizures.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Lamotrigine 2mg, 5mg, 25mg, 50mg 100mg and 200mg Dispersible Tablets outweighs the risks, hence Marketing Authorisations were granted.
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Module 6: Steps taken after initial procedure Not applicable
| **Product Name** | Lamotrigine 2mg Dispersible Tablets  
Lamotrigine 5mg Dispersible Tablets  
Lamotrigine 25mg Dispersible Tablets  
Lamotrigine 50mg Dispersible Tablets  
Lamotrigine 100mg Dispersible Tablets  
Lamotrigine 200mg Dispersible Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>GENERIC 10.1 (A) (III)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Lamotrigine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Dispersible Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>2mg, 5mg, 25mg, 50mg, 100mg and 200mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Clarendon Pharma Limited</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
</tbody>
</table>
| **CMS** | Lamotrigine 2mg Dispersible Tablets: BE, IE, NL, NO  
Lamotrigine 5mg Dispersible Tablets: BE, IE, IT, MT, NL, NO, PL, SI, SK  
Lamotrigine 25mg Dispersible Tablets: BE, CZ, DE, HU, IE, IT, MT, NL, NO, PL, SI, SK  
Lamotrigine 50mg Dispersible Tablets: BE, CZ, DE, HU, IE, IT, NL, NO, PL, SI, SK  
Lamotrigine 100mg Dispersible Tablets: BE, CZ, DE, HU, IE, IT, NL, NO, PL, SI, SK  
Lamotrigine 200mg Dispersible Tablets: BE, DE, IE, IT, NL, NO, SI |
| **Procedure Number** | UK/H/822/01-06 |
| **Timetable** | Day 90 – 19th December 2005 |
Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

Lamotrigine 2 mg Dispersible Tablets
Lamotrigine 5 mg Dispersible Tablets
Lamotrigine 25 mg Dispersible Tablets
Lamotrigine 50 mg Dispersible Tablets
Lamotrigine 100 mg Dispersible Tablets
Lamotrigine 200 mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of Lamotrigine.
Each tablet contains 5 mg of Lamotrigine.
Each tablet contains 25 mg of Lamotrigine.
Each tablet contains 50 mg of Lamotrigine.
Each tablet contains 100 mg of Lamotrigine.
Each tablet contains 200 mg of Lamotrigine.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible Tablet.

2mg
A round, white to off-white tablet, embossed with ‘LI’ over ‘2’ on one side and ‘>’ on the other side.

5mg
An oval, white to off-white tablet, embossed with ‘LI’ scoreline ‘5’ on one side and ‘>’ on the other side.

25mg
A shield-shaped, white to off-white tablet, embossed with ‘>’ over ‘LI25’ on one side and a scoreline on the other side.

50mg
A shield-shaped, white to off-white tablet, embossed with ‘>’ over ‘LI50’ on one side and a scoreline on the other side.
100mg
A shield-shaped, white to off-white tablet, embossed with ‘>’ over ‘LI100’ on one side and a scoreline on the other side.

200mg
A shield-shaped, white to off-white tablet, embossed with ‘>’ over ‘LI200’ on one side and a scoreline on the other side.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

Epilepsy:

*Adults and adolescents:*

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

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

*Adults and children over 2 years of age*

Add on therapy in:

- Partial epilepsy with or without generalisation
- Primary generalised epilepsy
- Lennox Gastaut syndrome if treatment with other available combinations of anti-epileptic drugs fail.

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

4.2. **Posology and method of administration**

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

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

When concomitant antiepileptic drugs are withdrawn to achieve monotherapy with lamotrigine 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 Section 4.5).

**Dosage in monotherapy:**

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

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

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

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

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

**Dosage in add-on therapy:**

**Adults and adolescents**
In patients taking valproate with/without any other 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 25-50 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100-200 mg/day given once a day or in two divided doses.

In those patients taking enzyme inducing 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 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400 mg/day given in two divided doses. Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

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

*Note: 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.

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, with a maximum dose of 200 mg/day.

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 1.2 mg/kg/day for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5-15 mg/kg/day given in two divided doses, with a maximum dose of 400 mg/day.

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

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

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

Note: 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.

**NOTE: If the calculated daily dose is 1–2 mg, then 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated dose 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.

**Adults and children over 2 years of age**
(Add-on therapy of Lennox-Gastaut syndrome if treatment with other available combinations of anti-epileptic drugs fail)

See above mentioned dosing schedules.

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

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

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

**Renal impairment**
Caution should be exercised when administering lamotrigine to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.4 and 5.2).
Combination with (continuous) oral hormonal contraceptives

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

The following situations may occur:

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

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

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

Pregnancy

See section 4.6.

Restarting therapy

The need for escalation to maintenance dose should be carefully assessed when restarting lamotrigine in patients who have discontinued it for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see section 4.4). The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see section 5.2), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy.
Method of administration:
Before administration the dispersible tablets should be dispersed in a sufficient amount of water until a homogeneous dispersion is achieved. Alternatively the tablets may be swallowed whole or may be chewed. The tablets have a scoreline for cosmetic purposes only and, therefore, should not be divided.

4.3. Contra-indications
Lamotrigine is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients.

4.4. Special warnings and special precautions for use
Due to possible cross-reactions, lamotrigine should be administered with special precaution in individuals with known hypersensitivity to carbamazepine and phenytoin.

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

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

The approximate incidence of serious skin rashes reported as SJS in adults and adolescents is 1 in 1000. The risk is higher in children under the age of 12 than in adults. Available data from a number of studies suggest the incidence of children under the age of 12 requiring hospitalisation due to rash ranges 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, which increases the mean half life of lamotrigine nearly two-fold (see Section 4.2).

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

Withdrawal of lamotrigine

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

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

Other organs

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

Folic acid metabolism

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

Use in combination with hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyloestradiol/levonorgestrel (30 µg/150 µg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold (see section 4.5). A decrease in lamotrigine plasma concentration was associated with loss of control of epileptic attacks. Following dose escalation, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. This has been
associated with dose-related unwanted effects. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. ‘pill-free week’), gradual transient increases in lamotrigine levels will occur during the week of inactive medication (see section 4.2). These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive medication. After starting the hormonal contraceptive medication again the lamotrigine levels will decrease. Variations in lamotrigine levels of this order are not recommended.

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

Other hormonal contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

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

**Renal impairment**

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

**Hepatic impairment**

In patients with 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.
Women of childbearing age

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

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 metabolized 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.

Effect of lamotrigine on the pharmacokinetics of other active substances

Antiepileptics

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

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

Hormonal contraceptives

Effect of lamotrigine on hormonal contraceptives:
In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinyloestradiol component of a combined hormonal contraceptive pill. A modest increase in overall clearance of the levonorgestrel component was observed. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.
Effect of other active substances on the pharmacokinetics of lamotrigine

Anti-epileptic agents which induce drug metabolising enzymes in the liver, (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (see section 4.2). Half-life of lamotrigine is shortened to approximately 14 hours, in children below 12 years: approximately 7 hours.

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

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

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

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

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

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

Hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine:
In a study of 16 female volunteers, 30 µg ethinyloestradiol/150 µg levonorgestrel in a combined hormonal contraceptive pill caused an approximately two-fold increase in lamotrigine overall clearance, resulting in
an average 52% and 39% reduction in lamotrigine AUC and $C_{\text{max}}$, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive treatment (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy. If the therapeutic effect of lamotrigine is uncertain although dose adjustments have been made a non-hormonal contraceptive method could be considered. Clinicians should exercise appropriate clinical management of women starting or stopping-hormonal contraceptives during lamotrigine therapy.

Psychoactive medicines

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

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

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

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

Folic acid

Interaction with folic acid metabolism (see sections 4.4 and 4.6). During prolonged human lamotrigine dosing, there were no significant changes in haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folic acid concentrations up to 1 year or red blood cell folic acid concentration up to 5 years.

4.6. Pregnancy and lactation

Pregnancy

As with other medicines, lamotrigine should only be used during pregnancy if the expected benefits outweigh the potential risks.
If women treated with lamotrigine plan to become pregnant, the indication of this product should be carefully considered. It is not recommended to stop anti-convulsive therapy during pregnancy since a loss of epileptic control is potentially life-threatening to both the mother and child.

**Risk related to epilepsy and antiepileptic drugs in general:**

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

**Risk linked to lamotrigine:**

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

Post marketing data from several prospective pregnancy registries have documented outcomes in over 1000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. The data do not suggest an increased risk of major birth defects compared to the general population. The data on use of lamotrigine in combination with other antiepileptic drugs are insufficient to assess whether the risk of malformation is increased. Therefore it is important, that pregnant women and women of childbearing potential practice monotherapy whenever possible.

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

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

**Lactation**

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

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

In clinical trials with lamotrigine undesirable effects of 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**

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

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

**Table 5: Undesirable Effects**

<table>
<thead>
<tr>
<th>Category</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin rash¹</td>
<td></td>
<td>Stevens Johnson syndrome</td>
<td>Toxic epidermal necrolysis</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Haematological abnormalities²</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity syndrome</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Irritability</td>
<td>Aggression</td>
<td></td>
<td>Tics, hallucinations, confusion</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Drowsiness, insomnia, tremor, nystagmus, ataxia</td>
<td></td>
<td>Agitation, unsteadiness, movement disorders, worsening of Parkinson’s disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency³</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, blurred vision</td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
<td></td>
</tr>
</tbody>
</table>
PAR Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Dispersible Tablets
UK/H/182/03-04

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Gastrointestinal disturbance, nausea, vomiting, diarrhoea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary disorders</td>
<td>Increased liver function tests, hepatic dysfunction, hepatic failure(^4)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Lupus-like reactions</td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>Tiredness</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

3There have been reports that lamotrigine may worsen parkinsonian symptoms in patients with pre-existing Parkinson’s disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients with this underlying condition.

4Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.

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

4.9. Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Antiepileptics

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

**Pharmacodynamics**
In tests designed to evaluate the central nervous system effects of 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 600 mg carbamazepine significantly impaired fine visual motor co-ordination and eye movements, while increasing both body sway and heart rate, whereas results with lamotrigine at doses of 150 mg and 300 mg did not differ from placebo.

### 5.2 Pharmacokinetic Properties

**Absorption**
Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations vary very little.

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

**Metabolism**
UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur.
Elimination
The mean steady state clearance in healthy adults is \(39 \pm 14\) 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.

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).

Special patient groups

Children
Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with sodium valproate alone (see Section 4.2).

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

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

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

5.3 Preclinical Safety

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

In rats an enhanced foetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (day 15-20). Animal experiments did not reveal impairment of fertility by lamotrigine.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Silica, colloidal anhydrous
Crocarmellose sodium
Povidone K30
Saccharin sodium
Talc
Magnesium stearate
Blackcurrant flavour (constituents including maltodextrin, gum arabic (E414), benzyl alcohol, triacetin, maltol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years
6.4 Special precautions for storage

2mg & 5mg tablets:
Store below 25°C

25mg, 50mg, 100mg & 200mg tablets:
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium Foil Blisters.

2mg
*Pack sizes 30 and 50 dispersible tablets.

5mg
*Pack sizes 14, 28, 30, 50, 56, 90 and 100 dispersible tablets.

25mg
*Pack sizes 21, 28, 30, 42, 50, 56, 90 and 100 dispersible tablets.

50mg
*Pack sizes 30, 42, 50, 56 and 90 dispersible tablets.

100mg
*Pack sizes 28, 50, 56, 90, 98, 100 and 200 dispersible tablets.

200mg
*Pack sizes 30, 50, 56, 90, 98, 100 and 200 dispersible tablets.

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
PATIENT INFORMATION LEAFLET

Lamotrigine 2 mg, 5 mg, 25 mg, 50 mg, 100 mg and 200 mg Dispersible Tablets

Read all of this leaflet carefully before you start taking this medicine. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally and you should NOT give it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
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. How to store Lamotrigine Dispersible Tablets

This leaflet refers to Lamotrigine Tablets or Lamotrigine Tablets with additional instructions. Your tablets are available in six strengths containing 2 mg, 5 mg, 25 mg, 50 mg, 100 mg and 200 mg of lamotrigine.

The active substance in your medicine is lamotrigine.

The other ingredients are microcrystalline cellulose, alpha-cyclodextrin, mannitol, colours (E129), croscarmellose sodium, magnesium stearate and blackcurrant flavour.

Marketing authorization holder:
Cipla UK Limited
16 King Street, Seagrave, Leicestershire LE2 7LY

Manufacturer:
...

Lamotrigine Tablets are not recommended for use in children under 2 years old.

If you have an allergy to lamotrigine, tell your doctor before you start taking it.

If you have taken too much Lamotrigine Tablets, contact your doctor or the nearest hospital casualty department immediately. Take the container and any remaining tablets with you so your doctor will know what you have taken.

If you forget to take your Lamotrigine Tablets at the right time, take
Module 4
Labelling
Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Dispersible Tablets

UK/H/182/03-04
Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Dispersible Tablets

UK/H/182/03-04
Module 5

Scientific discussion during initial procedure

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Lamotrigine 2mg, 5mg, 25mg, 50mg, 100mg & 200mg Dispersible Tablets in the treatment of epileptic seizures, could be approved. A national marketing authorisation was granted on 26th May 2005.

These mutual recognition applications concern generic versions of six tablet strengths of lamotrigine. The originator products are Lamictal Dispersible 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Tablets licensed to The Wellcome Foundation Ltd (United Kingdom) on 10/05/94.

The Marketing Authorisation Holder Clarendon Pharma Limited applied for marketing authorisations in the following CMS’s:

**Lamotrigine 2mg Dispersible Tablets:** BE, IE, NL, NO
**Lamotrigine 5mg Dispersible Tablets:** BE, IE, IT, MT, NL, NO, SI
**Lamotrigine 25mg Dispersible Tablets:** BE, CZ, DE, HU, IE, IT, MT, NL, NO, PL, SI, SK
**Lamotrigine 50mg Dispersible Tablets:** BE, CZ, DE, HU, IE, IT, NL, NO, PL, SI, SK
**Lamotrigine 100mg Dispersible Tablets:** BE, CZ, DE, HU, IE, IT, NL, NO, PL, SI, SK
**Lamotrigine 200mg Dispersible Tablets:** BE, DE, IE, IT, NL, NO, SI

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.

The objective of the development programme was to develop a globally acceptable, stable and bioequivalent tablet dosage form of lamotrigine comparable to Lamictal Dispersible Tablets licensed to The Wellcome Foundation.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
PHARMACEUTICAL ASSESSMENT

Drug substance

A detailed evaluation of the process, critical steps, process validation, process development and in-process controls were provided. Proof of structure has been elucidated for lamotrigine. The present lamotrigine fulfils ICH guidelines.

The analytical test methods used for the quality control of lamotrigine are appropriately described and validated. Compliance with the specifications has been shown.

Drug product

The objective of the development of this product has been a globally acceptable, stable and bioequivalent tablet dosage form of lamotrigine comparable to Lamictal Dispersible Tablets licensed to The Wellcome Foundation, UK. All the excipients used in the formulation comply with the Ph. Eur., with the exception of blackcurrant flavouring. The tablets are packed in blister strips of clear PVC/PVdC with a backing layer of aluminium. Bulk tablets are packaged in LDPE clear polyethylene bags within a polypropylene container. The bulk packaging materials are in compliance with EC 90/128.

The bioequivalence studies have been performed on Lamotrigine 5mg and 200mg Dispersible tablets against Lamictal 5mg and 200mg Dispersible Tablets, respectively. The biobatches were the same formulation and specification as that proposed for marketing. Comparative in-vitro dissolution data demonstrate that the products are pharmaceutically equivalent.

The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. The stability studies on the products have been undertaken according to ICH guidelines. As such, a shelf life of 24 months is acceptable for all strengths.

Drug Substance

The drug substance, lamotrigine is not the subject of a BP or PhEur monograph. The drug substance is very slightly soluble in water and slightly soluble in 0.1M HCl.

The drug product manufacturer tests the drug substance for appearance, identification, loss on drying, residue on ignition, heavy metals, assay, related substances, residual solvents and particle size

A reduced testing protocol is implemented for the batches of drug substance following successful qualification of the drug substance supplier in accordance with in-house qualification systems. The reduced testing protocol is as follows:
Appearance
Identification (IR and HPLC)
Loss on Drying
Residue on Ignition*
Heavy Metals*
Assay
Related substances
Residual solvents*
Particle size

*Not tested on a routine basis.

**Drug Product**

**Description and composition of the drug product**

The products are formulated as dispersible tablets containing the active pharmaceutical ingredient lamotrigine, at strengths of 2mg, 5mg, 25mg, 50mg, 100mg and 200mg per tablet. The excipients present are mannitol, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, povidone, saccharin sodium, blackcurrant flavour, talc purified and magnesium stearate.

The tablets are presented in PVC/PVDC/Aluminium Foil Blisters and in the following pack sizes:

**2mg**
*Pack sizes 30 and 50 dispersible tablets.

**5mg**
*Pack sizes 14, 28, 30, 50, 56, 90 and 100 dispersible tablets.

**25mg**
*Pack sizes 21, 28, 30, 42, 50, 56, 90 and 100 dispersible tablets.

**50mg**
*Pack sizes 30, 42, 50, 56 and 90 dispersible tablets.

**100mg**
*Pack sizes 28, 50, 56, 90, 98, 100 and 200 dispersible tablets.

**200mg**
*Pack sizes 30, 50, 56, 90, 98, 100 and 200 dispersible tablets

*Not all pack sizes may be marketed.

The six strengths of white to off-white tablets are differentiated by tablet shape, size and markings. Two bioequivalence studies have been performed, one on the 5mg strength and one on the 200mg strength in order to support the remaining tablet strengths.
Pharmaceutical Development

The objective of development rationale was to produce a product with characteristics similar to the originator product, Lamictal Tablets. Development studies were performed on the 5mg and the 200mg strength. The functions of ingredients are defined, and although the quantitative formulation differs from that of the brand leader, optimisation of the tablet formulation has been described. The final selected dissolution method for each strength of the proposed lamotrigine tablets versus each strength of Lamictal tablets (UK), shows profiles are similar. Batches subjected to dissolution studies showed similar dissolution profiles to the European brand leader products. Comparative impurity studies have also been undertaken in support of the claim of chemical essential similarity.

All tablets with a scoreline (all strengths apart from 2mg) passed the breakability test, in line with Ph.Eur requirements.

The relevant details were provided on the manufacturing process development.

No compatibility studies have been performed on the packaging materials, however stability studies show no incompatibility reactions.

Manufacture

The applicant confirms that all process validation batches and bioequivalence batches were manufactured at the development site. However, additional qualification data has been manufactured at the commercial manufacturing site. The applicant confirms that the equipment used and processes employed are those intended for the commercial product, and that process validation will be performed on the first three consecutive production scale batches at the named manufacturing site.

The manufacturing process involves dispensing, granulation, drying, milling, blending, and compression.

The environmental temperature and relative humidity are controlled during the commercial manufacture of the proposed dispersible tablet products.

Control of Excipients

The excipients are all PhEur compendial grade with the exception of blackcurrant flavour which is tested for appearance, loss on drying, bulk weight (untapped), arsenic lead and microbial contamination.

The origin of stearic acid in magnesium stearate is specified as being vegetable grade.

Control of Drug Product

The finished product specification of lamotrigine dispersible tablets includes tests for: appearance; hardness; thickness; friability; disintegration; fineness of dispersion; uniformity of dosage unit; identification by IR and HPLC; dissolution; assay; related substances for impurities and microbiological tests. The microbiological test is a non – routine one.
The finished product specification proposed is acceptable and the analytical methods used have been suitably validated. Analytical methods are provided for all tests including identification (HPLC and IR), assay (HPLC) related substances (HPLC), dissolution (UV). The method for fineness of dispersion is an in-house method in line with the Ph Eur.

Batch analysis data has demonstrated compliance with the proposed release specification.

Reference standards or materials

Working and reference standards certificates of analysis have been provided for the active and impurities from the active substance manufacturer.

Container Closure System

Lamotrigine dispersible tablets are packed in blister strips for the market. Blister packs comprise of blisters of clear PVC/PVdC with a backing layer of plain aluminium. The sources and specification of all packaging materials are specified supported by certificates of analysis. Packaging components comply with European directive 90/128/EEC, with respect to their suitability for contact with food.

Stability

Stability studies have been undertaken according to ICH guidelines.

The parameters monitored on stability are appearance, hardness, friability, disintegration, dissolution, related substances, assay, microbial contamination in line with ICH guidelines and using the methods of product release.

This stability data is satisfactory. These data support a shelf-life of 24 months.

Bioequivalence Studies

Bioequivalence studies have been performed on the 5mg and the 200mg tablet strength.

Samples were analysed using an adequately validated method. Pharmacokinetic parameters of $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$, $\text{C}_{\text{max}}$ and $\text{T}_{\text{max}}$ were determined and analysed.

The applications include several strengths i.e. 2mg, 5mg, 25mg, 50mg, 100mg and 200mg lamotrigine dispersible tablets. Results from the biostudies on the 5mg and 200mg strengths can be extrapolated to the other proposed tablet strengths.

Satisfactory Certificates of Analysis have been provided for the test and reference batches.
MAA Forms

MAA forms are provided. This is acceptable.

SPC

An SPC is provided for each strength of Lamotrigine dispersible tablets. This is acceptable.

Labelling and Leaflets

A combined leaflet for 2mg, 5mg, 25mg, 50mg, 100mg and 200mg dispersible tablets is presented. This is acceptable.

Information about the Expert

The pharmaceutical quality overall summary is written by a pharmacist with experience in the Pharmaceutical industry.

Quality Overall Summary

An adequate quality overall summary is provided by the quality expert.

Pharmaceutical Conclusions

It is recommended that marketing authorisations are granted for these applications. The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition similar dissolution profiles have been demonstrated for the proposed and reference products.
NON CLINICAL ASSESSMENT

These applications for a generic product claim essential similarity to Lamictal Dispersible 2mg, 5mg, 25mg, 50mg, 100mg and 200mg Tablets licensed to The Wellcome Foundation Ltd (United Kingdom), which has been licensed within the UK for over 10 years.

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

Clinical Pharmacology

Clinical trials support the established indications for this product. A literature search from the last major published review in 1995 to the present has been conducted in order to establish that there are no recent reports which might call the efficacy into question. Likewise a general overview of the safety is given and is supplemented by a literature search from 1995 to present to detect any recent ADRs or safety findings which may be of concern. Finally, the bioequivalence aspects of the product are considered in detail.

Overview of Biopharmaceutics

The relative oral bioavailability of Lamotrigine 5mg and 200mg dispersible tablets and the European brand lead Lamictal™ 5mg and 200mg dispersible tablets have been established by comparing the single-dose pharmacokinetics of lamotrigine from these two formulations in two separate studies.

Lamotrigine 5mg dispersible tablets

The relative oral bioavailability of Lamotrigine 5mg dispersible tablets (manufactured at the development site) and the European brand leader Lamictal™ 5mg dispersible tablets (manufactured by GlaxoSmithKline, UK and sourced in France) was established by comparing the single-dose pharmacokinetics of lamotrigine from the two formulations, under fasting conditions, in a randomised crossover study.

The design employed is appropriate for establishing bioequivalence of compounds such as lamotrigine, which do not exhibit complicated pharmacokinetics. As lamotrigine demonstrates linear, dose-proportional pharmacokinetics over the dose range 30-450mg, the selection of a specific study to examine the bioequivalence of the 5mg tablet given at a dose below this range is also appropriate.

The study was conducted according to Good Clinical Practice. A total of 23 healthy male subjects participated in the study.

Each subject received either 4 x 5mg lamotrigine generic dispersible tablets (Test) or 4 x 5mg Lamictal™ dispersible tablets (Reference), swallowed whole with 240ml of water after an overnight fast, according to a computer generated randomisation list. Following a three-week washout period, the subjects received the alternative formulation under identical conditions.

A total of 21 subjects completed the study and were included in the statistical analysis. Two subjects withdrew prior to the second treatment period for personal reasons.

The comparisons between the log-transformed AUC and Cmax data for the Test and Reference formulations are given below.
Bioequivalence Results for Lamotrigine

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST</th>
<th>REFERENCE</th>
<th>LOWER</th>
<th>UPPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>250.12</td>
<td>253.27</td>
<td>100.48</td>
<td>108.63</td>
</tr>
<tr>
<td>AUC₀–₄</td>
<td>9482.30</td>
<td>9523.40</td>
<td>101.31</td>
<td>109.83</td>
</tr>
<tr>
<td>AUC₀–∞</td>
<td>10,940.59</td>
<td>10,978.21</td>
<td>100.78</td>
<td>108.31</td>
</tr>
</tbody>
</table>

Cmax: ng/ml
AUC₀–₄: ng.h/ml
AUC₀–∞: ng.h/ml

The geometric 90% confidence intervals for the ratios of AUC₀–₄, AUC₀–∞ and Cmax for the Test and Reference formulations fall wholly within the internationally accepted range for bioequivalence of 80 to 125%.

The mean Tmax for the Test formulation (1.50 ± 0.77 hours) was similar to that of the Reference formulation (1.53 ± 0.95 hours), indicating no difference in the rate of absorption.

EFFICACY

No new data.

SAFETY

No new data.

EXPERT REPORTS

CTD

PATIENT INFORMATION LEAFLET (PIL)

Satisfactory

LABELLING

Satisfactory
APPLICATION FORM (MAA)

Satisfactory

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory. Fully consistent with originator SPC

MEDICAL CONCLUSION

Marketing authorisation is recommended.