

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0966/016/005

Case No: 2054755

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Ergha Healthcare Ltd

Damastown, Mulhuddart, Dublin 15

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Bymot 100 mg Dispersible Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/02/2009** until **24/08/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bymot 100 mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 100 mg lamotrigine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet

White to off white, round tablet, debossed with the number “100” on one side and “DLT” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy

Adults and adolescents aged 13 years and above

- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.
- Seizures associated with Lennox-Gastaut syndrome. Lamotrigine is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

Children and adolescents aged 2 to 12 years

- Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.
- Monotherapy of typical absence seizures.

4.2 Posology and method of administration

Lamotrigine dispersible/chewable 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.

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.

Epilepsy

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

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

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

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

regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	(once a day)	(once a day)	day or two divided doses) To achieve maintenance, doses may be increased by maximum of 50 - 100 mg every one to two weeks until optimal response is achieved
In patients taking medicinal products where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.			

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

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dose
Monotherapy of typical absence seizures:	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1 – 10 mg/kg/day, although some patients have required higher doses (up to 15 mg/kg/day) to achieve desired response (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg/day every one to two weeks until optimal response is achieved
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see section 4.5):			
This dosage regimen should be used with valproate regardless of any other concomitant medicinal products	0.15 mg/kg/day* (once a day)	0.3 mg/kg/day (once a day)	1 – 5 mg/kg/day (once a day or two divided doses) To achieve maintenance, doses may be increased by maximum of 0.3 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 200 mg/day
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see section 4.5):			
This dosage regimen should	0.6 mg/kg/day (two divided	1.2 mg/kg/day (two divided	5 – 15 mg/kg/day

be used without valproate but with:	doses)	doses)	(once a day or two divided doses)
phenytoin			To achieve maintenance, doses may be increased by maximum of 1.2 mg/kg every one to two weeks until optimal response is achieved, with a maximum maintenance dose of 400 mg/day
carbamazepine			
phenobarbitone			
primidone			
rifampicin			
lopinavir/ritonavir			

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

This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	0.3 mg/kg/day (once a day or two divided doses)	0.6 mg/kg/day (once a day or two divided doses)	1 – 10 mg/kg/day (once a day or two divided doses)
			To achieve maintenance, doses may be increased by maximum of 0.6 mg/kg every one to two weeks until optimal response is achieved, with a maximum of maintenance dose of 200 mg/day

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

2 mg dispersible/chewable tablets - where this is the lowest marketed strength: <* If the calculated daily dose in patients taking valproate is 1 mg or more but less than 2 mg, then lamotrigine 2 mg dispersible/chewable tablets 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.>

5 mg dispersible/chewable tablets - where 2mg dispersible/chewable tablets are not marketed and lamotrigine 5mg dispersible/chewable tablets are the lowest marketed strength: <* If the calculated daily dose in patients taking valproate is 2.5 mg or more but less than 5 mg, then lamotrigine 5 mg dispersible/chewable tablets may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 2.5 mg, then lamotrigine should not be administered.

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

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

5 mg dispersible/chewable tablets – where 2 mg dispersible/chewable tablets are not marketed and 5 mg dispersible/chewable tablets are the lowest marketed strength:

It should be noted that with the currently available lamotrigine 5 mg dispersible/chewable tablet strength, it is not possible to accurately initiate lamotrigine therapy using the recommended dosing guidelines in paediatric patients weighing less than 17 kg.

Children below 2 years

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

General dosing recommendations for lamotrigine in special patient populations

Women taking hormonal contraceptives

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

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

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

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

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

Starting lamotrigine in patients already taking hormonal contraceptives

Dose escalation should follow the normal dose recommendation described in the tables.

Starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation

Adjustment to the recommended maintenance dose of lamotrigine may not be required.

Elderly (above 65 years)

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

Renal impairment

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

Hepatic impairment

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening rashes such as Stevens–Johnson syndrome and toxic epidermal necrolysis (see section 4.8).

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

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

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

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

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

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

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

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

Clinical worsening and suicide risk

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

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

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

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

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

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

Effects of lamotrigine on hormonal contraceptive efficacy

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

Dihydrofolate reductase

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

Renal failure

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

Patients taking other preparations containing lamotrigine

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

Development in children

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

Precautions relating to epilepsy

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

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

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

Myoclonic seizures may be worsened by lamotrigine.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Table 3: Effects of other medicinal products on glucuronidation of lamotrigine

Medicinal products that significantly inhibit glucuronidation of lamotrigine	Medicinal products that significantly induce glucuronidation of lamotrigine	Medicinal products that do not significantly inhibit or induce glucuronidation of lamotrigine
Valproate	Phenytoin	Oxcarbazepine
	Carbamazepine	Felbamate
	Phenobarbitone	Gabapentin
	Primidone	Levetiracetam
	Rifampicin	Pregabalin
	Lopinavir/ritonavir	Topiramate
	Ethinylloestradiol/ levonorgestrel combination*	Zonisamide

		Lithium
		Bupropion
		Olanzapine

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

Interactions involving antiepileptic drugs

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

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

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

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

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

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

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

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

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

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

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

Interactions involving other psychoactive agents

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

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

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

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

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

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

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

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylloestradiol 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 C_{max}, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicinal products

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

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

4.6 Pregnancy and lactation

Risk related to antiepileptic drugs in general

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

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

Risk related to lamotrigine

Pregnancy

Epidemiological studies involving in total approximately 2000 women exposed to lamotrigine monotherapy during pregnancy cannot exclude an increased risk for congenital malformations. One registry has reported an increased incidence of facial clefts. Other data sets have not confirmed this finding. Animal studies have shown developmental toxicity (see section 5.3).

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

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

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

Lactation

Data indicate that lamotrigine passes into breast milk. In some breast-fed infants, 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. Should a woman decide to breast-feed while on therapy with lamotrigine, the infant should be monitored for adverse effects.

Fertility

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

4.7 Effects on ability to drive and use machines

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

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

Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

4.8 Undesirable effects

The undesirable effects have been divided into sections based on the data currently available.

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

Very common (>1/10),
 Common (>1/100, <1/10),
 Uncommon (>1/1000, <1/100),
 Rare (>1/10,000, <1/1000),
 Very rare (<1/10,000).

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

Epilepsy

Blood and lymphatic system disorders

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

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

Immune system disorders

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

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

Psychiatric disorders

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

Nervous system disorders

During monotherapy clinical trials:

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

During other clinical experience:

Very common: somnolence, ataxia, dizziness, headache.
 Common: nystagmus, tremor, insomnia.
 Very rare: agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency.

There have been reports that lamotrigine may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders

During monotherapy clinical trials:

Uncommon: diplopia, blurred vision.

During other clinical experience:

Very common: diplopia, blurred vision.

Rare: conjunctivitis.

Gastrointestinal disorders

During monotherapy clinical trials:

Common: nausea, vomiting, diarrhoea.

During other clinical experience:

Very common: nausea, vomiting.

Common: diarrhoea.

Hepato-biliary disorders

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

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

Skin and subcutaneous tissue disorders

Very common: skin rash.

Rare: Stevens–Johnson Syndrome.

Very rare: toxic epidermal necrolysis.

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

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

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

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

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

Musculoskeletal and connective tissue disorders

Very rare: lupus-like reactions.

General disorders and administration site conditions

Common: tiredness.

4.9 Overdose

Symptoms and signs

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiepileptics,
ATC code: N03AX09.

Mechanism of action

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

Pharmacodynamic effects

In tests designed to evaluate the central nervous system effects of medicinal products, 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.

Clinical efficacy and safety in children aged 1 to 24 months

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

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

Clinical efficacy and safety in Lennox-Gastaut syndrome

There are no data for monotherapy in seizures associated with Lennox-Gastaut syndrome.

Study of the effect of lamotrigine on cardiac conduction

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

5.2 Pharmacokinetic propertiesAbsorption

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

Distribution

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

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

Metabolism

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

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

Elimination

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

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

Linearity

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

Special patient populationsChildren

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

Infants aged 2 to 26 months

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

Elderly

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

Renal impairment

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

Hepatic impairment

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

5.3 Preclinical safety data

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Cellulose microcrystalline
Sodium starch glycolate (Type A)
Maize starch pregelatinised
Croscarmellose sodium
Silica colloidal anhydrous
Sodium stearyl fumarate
Saccharin sodium
Artificial Cherry Flavour (constituents include modified food starch (E1450))

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Transparent PVC/PVdC/aluminium blisters
Transparent PVC/PE/PVdC/aluminium blisters
Blisters in cardboard boxes containing : 28, 30, 50, 56, 60, 90, 100 and 200 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ergha Healthcare Ltd.
Damastown
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Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA966/16/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25th August 2006

10 DATE OF REVISION OF THE TEXT

November 2008