IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0967/012/002
Case No: 2037874

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

Ranbaxy (UK) Limited

20 Balderton Street, **London W1K 6TL**, **United Kingdom**

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

Lamotrigine Ranbaxy 50 mg 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 **14/12/2007** until **11/10/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lamotrigine Ranbaxy 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg lamotrigine
Excipients: 5.94 mg of lactose, 0.42 mg of sodium

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Yellow coloured, capsule shaped, biconvex tablets debossed with ‘L’ and ‘50’ on either side of the score line on one side and a deep breakline on the other side. The tablet can be divided into equal halves.

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.

Add on therapy in epilepsy:
- Partial seizures
- Generalised seizures:
    - primary seizures
    - secondary tonic-clonic seizures
- Seizures associated with Lennox-Gastaut syndrome when other available anti-epileptic agent combinations fail.

Children over 2 years of age
Add-on therapy in:
- Partial seizures
- Seizures associated with Lennox-Gastaut syndrome if treatment with other available combinations of antiepileptic agents fails.

4.2 Posology and method of administration

Administration

Lamotrigine tablets can be divided into to halves or can be taken whole with a little water, and should be taken as far as possible at the same time every day on an empty stomach or with a meal.

To ensure a therapeutic dose is maintained the weight of a patient must be monitored and the dose reviewed as weight changes occur. If a calculated dose of lamotrigine (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

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

When concomitant antiepileptic drugs are withdrawn to achieve Lamotrigine monotherapy or other antiepileptic drugs (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 over 12 years (see Table 1)

The initial Lamotrigine dose in monotherapy is 25mg once a day for two weeks, followed by 50mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50mg-100mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 - 200mg/day given once a day or as two divided doses. Some patients have required 500mg/day of Lamotrigine to achieve the desired response.
The initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash (see section 4.4).

Children aged 2 to 12 years

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

Dosage in add-on therapy

Adults and adolescents over 12 years (see Table 1)

In patients taking valproate with/without any other anti-epileptic drug (AED) the initial Lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25-50 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 100mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400mg/day given in two divided doses. Some patients have required 700 mg/day of Lamotrigine to achieve the desired response.

In those patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial lamotrigine dose is 25mg once a day for two weeks, followed by 50mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50-100mg every1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100-200mg/day given once a day or in two divide doses.

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

Treatment regimen		Weeks 1 + 2	Weeks 3 + 4	Usual Maintenance Dose
Monotherapy		25 mg (once a day)	50 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks
Add-on therapy with valproate regardless of any concomitant medications		12.5 mg (given 25 mg on alternate days)	25 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25 – 50 mg every one to two weeks
Add-on therapy without valproate	This dosage regimen should be used with: phenytoin carbamazepine phenobarbital primidone or with other inducers of lamotrigine glucuronidation (see section 4.5).	50 mg (once a day)	100 mg (two divided doses)	200 – 400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every one to two weeks
Oxcarbazepine without other enzyme inducers or inhibitors See section 4.5	25 mg (once a day)	50 mg (once a day)		100-200mg (once a day or two divided doses).To achieve maintenance, doses maybe increased by 50-100mg every1-2 weeks
Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.				

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

Children aged 2 to 12 years

In patients taking valproate with / without any other anti-epileptic drug (AED), the initial Lamotrigine dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg/day given once a day or in two divided doses, with a maximum dose of 200 mg/day.

In those patients taking enzyme inducing AED's with/without other AED's (except valporate) 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 0.3mg/kg body weight/day given once a day or in two divided doses for two weeks, followed by 0.6mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6mg/kg every1-2weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-10mg/kg/day given once a day or in two divided doses, with a maximum dose of 200mg/day.

Table 2. Recommended treatment regimen of Lamotrigine for children aged 2-12 years on combined drug therapy (Total daily dose in mg/kg bodyweight/day)

Treatment regimen		Weeks 1 + 2	Weeks 3 + 4	Usual Maintenance Dose
Add-on therapy with valproate regardless of any other concomitant medication		0.15 mg/kg* (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses) up to a maximum dose of 200mg/day.
Add-on therapy without valproate	This dosage regimen should be used with: phenytoin carbamazepine phenobarbital primidone or with other inducers of lamotrigine glucuronidation (see section 4.5).	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (two divided doses) up to a maximum dose of 400mg/day.
Oxcarbazepine without other enzyme inducers or inhibitors		0.3mg/kg (once a day or in two divided doses)	0.6mg/kg (once a day or in two divided doses)	0.6mg/kg increments every1-2weeks to achieve a maintenance dose of 1-10mg/kg (once a day or in two divided doses), up to a maximum dose of 200mg/day

Note: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used, thereafter, the dose should be increased until optimal response is achieved.

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

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 agents fail)See above-mentioned dosing schedules.
For prescribed doses not realisable/practicable with this medicinal product, other medicinal products containing lamotrigine are available in other strengths.

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 recommended schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly population.

Hepatic impairment

Initial, escalation and maintenance doses should 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. Depending on the dose, the recommended dose may not be performable in patients with hepatic impairment with the current strengths of this medicinal product (see section 5.2).

Renal impairment

Caution should be exercised when administering lamotrigine to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicinal products; reduced maintenance doses maybe 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 base line 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 adverse 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 50-100mg a week over a period of 3weeks.

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

Pregnancy

See section 4.6.

Restarting Therapy

Prescribers should carefully assess the need for escalation to maintenance dose when restarting lamotrigine in patients who have discontinued it, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for lamotrigine (see section 4.4). Restarting treatment is not recommended when lamotrigine was withdrawn because of rush.
The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing lamotrigine exceeds five half-lives (see section 5.2), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule, as though initiating therapy (see section 4.2).

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

4.3 Contraindications

This medicinal product is contraindicated in patients with hypersensitivity to lamotrigine or to any of the excipients of the medicinal product.

4.4 Special warnings and 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 in children under the age of 12 is higher than in adults. Available data from a number of studies suggest that the incidence of rashes associated with hospitalisation in children under the age of 12 is from 1 in 300 to 1 in 100 (see section 4.8).

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

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

Effects of hormonal contraceptives on lamotrigine efficacy:
An ethinyloestradiol/levonorgestrel (30mcg/150mcg) 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) maybe needed to attain a maximal therapeutic response. When stopping hormonal contraceptives, the clearance of lamotrigine maybe 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 treatment (e.g.' pill-free week'), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (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 treatment. After starting the hormonal contraceptive treatment 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 medicinal product. Other hormonal contraceptive and hormone replacement therapy (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 follicle-stimulating hormone (FSH) and luteinising hormone (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 the premenstrual pattern, e.g. break through 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 moderate (child-Pugh grade B) and 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 child bearing age
Women of child bearing age and during pregnancy should use anticonvulsants as monotherapy whenever possible, since the risk of malformations maybe enhanced in combination therapy with other anticonvulsants.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Although changes in the plasma concentrations of other antiepileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma 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 300mg lamotrigine had no effect on the pharmacokinetics of the ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed. Measurement of serum follicle-stimulating hormone (FSH), luteinising hormone (LH) and estradiol 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). Vaginal bleeding was reported by some volunteers (see section 4.4). The effects of doses of lamotrigine other than 300mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Effects of other active substances on the pharmacokinetics of lamotrigine:

Antiepileptic agents which induce drug-metabolising enzymes (such as phenytoin, carbamazepine, phenobarbital and primidone) enhance the metabolism of lamotrigine and may increase dose requirements (sec section 4.2). The 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. The half-life of lamotrigine is extended to approx. 70 hours; in children below 12 years, 45-55 hours.

Table 3 Effects of other drugs on glucuronidation of lamotrigine

Active substances that significantly inhibit glucuronidation of lamotrigine	Active substances that significantly induce glucuronidation of lamotrigine	Active substances that do not significantly inhibit of induce glucuronidation of lamotrigine
Valproate	Carbamazepine	Lithium
	Phenytoin	Bupropion
	Primidone	Olanzapine
	Phenobarbital	Oxczrbazepine**
	Rifampicin***	
	Ethinylestradiol/ levonorgestrel combination*	

*Other hormonal contraceptives and hormone replacement therapy have not been studied; they may similarly affect lamotrigine pharmacokinetic parameters.

**In a study in healthy adult volunteers using doses of 200mg/day lamotrigine and 1200mg/day oxcarbazepine, results showed that compared with placebo, the mean values for steady state peak plasma concentration (C_{max}) and area under the curve (AUC_{0-24}) of lamotrigine were reduced by 2% and 8%, respectively. The 90% confidence intervals indicated that the differences were between -22% and +8% for AUC_{0-24} and-15% and +15% for C_{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 mcg ethinylestradiol/150 mcg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and C_{max}, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy.

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 100mg/day lamotrigine.
In a study in healthy adult volunteers, 15mg olanzapine reduced the AUC and Cmax of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200mg 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, orserumor 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

Risk related to antiepileptic drugs in general
Specialist advice should be given to women who are of childbearing potential. The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. Discontinuation of antiepileptic therapy should be avoided as this may lead to breakthrough seizures which could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptics 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.

Multiple antiepileptic drug therapy is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to lamotrigine
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 embryofoetal damage by reducing folic acid levels. Intake of folic acid (in the usual dose for pregnant women) when planning pregnancy and during early pregnancy is strongly recommended.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine plasma levels and loss of seizure control 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 around 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

There is limited information on the use of lamotrigine during breast feeding.
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 breastfeed only after a careful risk-benefit assessment for the infant or stop breast feeding. 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 adverse events of a neurological character such as dizziness and diplopia have been reported. As there is individual variation in response to all antiepileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

4.8 Undesirable effects

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), not known (cannot be estimated from the available data)

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Blood and lymphatic system disorders					Haematologica labnormalities [2]

Nervous system disorders	Headache, dizziness	Drowsiness, insomnia, tremor, nystagmus, ataxia			Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis, increase in seizure frequency [3]
Eye disorders	Diplopia, blurred vision			Conjunctivitis	
Gastrointestinal disorders		Gastrointestinal disturbance, nausea, vomiting, diarrhoea			
Skin and subcutaneous tissue disorders	Skin rash[1]			Stevens Johnson syndrome	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders					Lupus-like reactions
General disorders and administration site conditions		Tiredness			
Immune system disorders					Hypersensitivity syndrome
Hepato-biliary disorders					Increased liver function tests, hepatic dysfunction, hepatic failure [4]
Psychiatric disorders		Irritability	Aggression		Tics, hallucinations, confusion

[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 hospitalization 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) maybe 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.
[2]Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis) may or may not be associated with the hypersensitivity syndrome.
[3]There have been reports that lamotrigine may worsen parkinsonian symptoms in patients with pre-existing Parkinson's disease, and isolated reports of extrapyramidal effects and choreoathetosis inpatients without this underlying condition.
[4]Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.
There are insufficient data available about the effect of lamotrigine on growth, development and cognitive functions of children.

4.9 Overdose

Symptoms 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 an overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacokinetic group: Other antiepileptics **ATC code: N03AX09**

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 neurons and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

Pharmacodynamics

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

In another study, single oral doses of 600mg carbamazepine significantly impaired fine visual motor co-ordination and eye movements, while increasing both body sway and heart rate, whereas results with lamotrigine at doses of 150mg and 300mg did not differ from placebo.

5.2 Pharmacokinetic properties

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

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 ± 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 150mg single dose revealed that average plasma clearance was about 37% lower in the elderly. However the mean clearance in the elderly (0.39 ml/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 ml/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg.

A population pharmacokinetic analysis with both young and elderly subjects (including 12 elderly volunteers from the pharmacokinetic study and 13 elderly epilepsy patients enrolled in monotherapy clinical trials) indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35ml/min at age 20 to 31 ml/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37ml/min between the young and elderly groups. To date there have been no specific studies of lamotrigine pharmacokinetics in elderly patients with epilepsy.

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 data

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 maternal toxicity, the teratogenic potential of lamotrigine has not been characterised above clinical exposure.

In rats, enhanced foetal as well as postnatal mortality was observed when lamotrigine was administered later during gestation (day 15-20). These effects were observed at the expected clinical exposure.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycollate (Type A)
Lactose monohydrate
Povidone K-30
Magnesium stearate
Colloidal anhydrous silica
Talc
Yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/ PVdC/ aluminium foil blisters containing 7, 14, 21, 28, 30, 56 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 967/12/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT