Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lamotrigine 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg lamotrigine.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round, flat, bevelled edged tablets with a score on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy
Adults:
Lamotrigine is indicated for use as adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome.

Children:
Lamotrigine is indicated as adjunctive therapy in the treatment of epilepsy, for partial seizures and generalised seizures including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome.

Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended.

After epileptic control has been achieved during adjunctive therapy, concomitant anti-epileptic drugs (AEDs) may be withdrawn and patients continued on Lamotrigine monotherapy.

Bipolar Disorder (Adults 18 years of age and over)
Lamotrigine is indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

4.2 Posology and method of administration

EPILEPSY

Dosage in Epilepsy monotherapy

Adults (over 12 years of age):
The initial lamotrigine dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 - 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 - 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of lamotrigine to achieve the desired response.

Table 1: Recommended dose escalation in Epilepsy for adults (over 12 years of age) on monotherapy.

Weeks 1+2	**Weeks 3+4**	Maintenance Dose
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 50-100mg every 1-2 weeks

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see 4.4 *Special Warnings and Special Precautions for Use*).

Dosage in Epilepsy add-on therapy

Adults (over 12 years of age):
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 AEDs with/without other AEDs (except valproate), the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-500 mg/day given in two divided doses.

Some patients have required 700 mg/day of lamotrigine to achieve the desired response.

In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see 4.5 *Interaction with Other Medicinal Products and Other Forms of Interaction*), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

Table 2: Recommended dose escalation in Epilepsy for adults (over 12 years of age) on combined drug therapy.

	Weeks 1 + 2	**Weeks 3 + 4**	**Maintenance Dose**
Valproate with/without any other AEDs	12.5 mg (given 25 mg 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 25-50mg every 1-2 weeks
Enzyme inducing AEDs* with/without other AEDs (except valproate)	50 mg (once a day)	100 mg (two divided doses)	200-500 mg (two divided doses) To achieve maintenance, doses may be increased by 100mg every 1-2 weeks
* e.g. phenytoin, carbamazepine, phenobarbitone and primidone.			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.			

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see 4.4 *Special Warnings and Special Precautions for Use).*

Children (2 to 12 years of age):
In patients taking valproate with/without any other 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 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 of 200

mg/day.

In those patients taking enzyme inducing AEDs with/without other AEDs (except valproate), the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day given in two divided doses 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 of 400 mg/day.

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

In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see 4.5 *Interaction with Other Medicinal Products and Other Forms of Interaction*), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.

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

	Weeks 1 + 2	**Weeks 3 + 4**	**Maintenance Dose**
Valproate with/without any other AEDs	0.15mg/kg ** (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1-5 mg/kg (once a day or two divided doses) to a maximum of 200mg/day
Enzyme inducing AEDs* with/without other AEDs (except valproate)	0.6mg/kg (two divided doses)	1.2mg/kg (two divided doses)	1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5-15 mg/kg (two divided doses) to a maximum of 400mg/day
* e.g. phenytoin, carbamazepine, phenobarbitone and primidone.			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.			

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

Because of a risk of rash the initial dose and subsequent dose escalation should not be exceeded (see 4.4 *Special Warnings and Special Precautions for use*).
It is likely that patients aged 2-6 years will require a maintenance dose at the higher end of the recommended range.

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

General Dosing Recommendations for Epilepsy:
When concomitant anti-epileptic drugs are withdrawn to achieve lamotrigine monotherapy or other anti-epileptic drugs (AEDs) are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see 4.5 *Interaction with Other Medicinal Products and Other Forms of Interaction*).

BIPOLAR DISORDER

Lamotrigine is recommended for use by bipolar patients in the prevention of mood episodes, predominantly for those patients at risk of a future depressive episode. Adjunctive therapy, if clinically indicated, should be considered for the prevention of manic episodes, as efficacy with lamotrigine in mania has not been conclusively established.
Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see 4.4 *Special Warnings and Precautions for Use*).
The following transition regimen should be followed to prevent depressive episodes. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks (see Table 4, below) after which other psychotropic and/or anti-epileptic drugs can be withdrawn, if clinically indicated (see Table 5).

Table 4: Recommended dose escalation to the maintenance total daily stabilisation dose for adults (over 18 years of age) treated for Bipolar Disorder.

Treatment Regimen	**Weeks 1-2**	**Weeks 3-4**	**Week 5**	**Target Stabilisation Dose (Week 6)****
a) Adjunct therapy to drugs with no clinical pharmacokinetic interaction with lamotrigine e.g. lithium, OR Monotherapy with lamotrigine	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200mg Range 100-400mg (once a day or two divided doses)
b) Adjunct therapy with Enzyme inhibitors e.g. Valproate	12.5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg Maximum daily dose of 200 mg (once a day or two divided doses)
c) Adjunct therapy with Enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking Valproate	50 mg (once a day or two divided doses)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
NOTE: In patients taking psychotropic medicines where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.				

**The Target stabilisation dose will alter depending on clinical response.

a) Adjunct therapy to drugs with no clinical pharmacokinetic interaction with lamotrigine e.g. lithium, OR Monotherapy with lamotrigine.

The initial lamotrigine dose in patients taking concomitant drugs with no known/theoretical pharmacokinetic interaction with lamotrigine or in monotherapy, is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100-400 mg was used in clinical trials.

b) Adjunct therapy with Enzyme inhibitors e.g. Valproate.

In patients taking enzyme inhibiting concomitant drugs such as valproate the initial lamotrigine dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. The dose should be increased to 50 mg once

a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.

c) Adjunct therapy with Enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking Valproate.

In those patients taking enzyme inducing drugs such as carbamazepine or phenobarbitone and NOT taking 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. The dose should be increased to 200 mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day in two divided doses however, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses which may be given from week 7.

Other psychotropic medications may be withdrawn gradually, if clinically indicated. If the target daily maintenance dose has been achieved, the dosage schedule below can be used as a guide to withdraw other psychotropic medications (see table 5).

Table 5: Withdrawal of concomitant psychotropic drugs in Bipolar Disorder if the maintenance stabilisation dose has been achieved.

Treatment Regimen	**Week 1**	**Week 2**	**Week 3 onwards***
(a) Following withdrawal of psychotropic or AED drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (Range 100-400 mg)		
(b) Following withdrawal of enzyme inhibitors e.g. valproate	Double the stabilisation dose, not exceeding 100 mg/week i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day	Maintain this dose (200 mg/day) (two divided doses)	
(c) Following withdrawal of enzyme inducers e.g. carbamazepine depending on original dose**	400 mg **	300 mg	200 mg
	300 mg**	225 mg	150 mg
	200 mg**	150 mg	100 mg
NOTE: In patients taking psychotropic medications where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.			

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

(a) Following withdrawal of adjunct therapy with psychotropic or anti-epileptic drugs with no pharmacokinetic interaction with lamotrigine e.g. lithium:

The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

(b) Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate:
The dose of lamotrigine should be increased to double the original target stabilisation dose and maintained at this, once valproate has been terminated.

(c) Following withdrawal of adjunct therapy with enzyme inducers e.g. carbamazepine, depending on original maintenance dose:
The dose of lamotrigine should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

Adjustment of lamotrigine daily dosing in patients with Bipolar Disorder following addition of other medications:
Based on drug interaction studies, the following recommendations can be made (see Table 6, below):

Table 6: Adjustment of lamotrigine daily dosing in patients with Bipolar Disorder following the addition of other medications.

Treatment Regimen	**Current lamotrigine Stabilisation dose (mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
(a) Following withdrawal of psychotropic or AED drugs with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (range 100-400 mg)			
(b) Addition of enzyme inhibitors e.g. valproate, depending on original dose of lamotrigine	200 mg	100 mg	Maintain this dose (100 mg/day)	
	300 mg	150 mg	Maintain this dose (150 mg/day)	
	400 mg	200 mg	Maintain this dose (200 mg/day)	
(c) Addition of enzyme inducers e.g. carbamazepine in patients NOT taking valproate and depending on original dose of lamotrigine	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
NOTE: In patients taking psychotropic medicines where the pharmacokinetic interaction with lamotrigine is currently not known, the dose adjustment as recommended for lamotrigine with concurrent valproate, should be used.				

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

Children (less than 18 years of age):
Safety and efficacy of lamotrigine in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.
If a calculated dose of lamotrigine (e.g. for use in children (epilepsy only) or patients with hepatic impairment) cannot be divided into multiple lower strength tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

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

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

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' concomitants medications; reduced maintenance doses may be effective for patients with significant renal functional impairment. (see 4.4 *Special Warnings and Precautions for Use*). For more detailed pharmacokinetic information see 5.2. *Pharmacokinetic Properties.*

4.3 Contraindications

Lamotrigine is contra-indicated in individuals with known hypersensitivity to lamotrigine.

4.4 Special warnings and precautions for use

This product contains a novel active ingredient and is presently on intensive monitoring. Any side effects or unusual response encountered with the drug should be reported immediately to the patient's consultant during the intensive monitoring period and thereafter to the Irish Medicines Board.

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine (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 including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see 4.8 *Undesirable Effects*).

In adults enrolled in studies utilising 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 SJS (1 in 1000).

In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000.

The risk of serious skin rashes in children is higher than in adults.

Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in epileptic children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash can be mistaken for an infection, physicians should consider the possibility of a 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 4.2

Posology and Method of Administration).

- Concomitant use of valproate, which increases the mean half-life of lamotrigine nearly two fold (see 4.2 *Posology and Method of Administration*).

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 (see *4.8 Undesirable Effects)*. 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. If such signs and symptoms are present the patient should be evaluated immediately and lamotrigine discontinued if an alternative aetiology cannot be established.

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.

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.

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

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 2 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.

Bipolar Disorder:
The possibility of a suicide attempt is inherent in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that lamotrigine causes clinically significant induction or inhibition of hepatic oxidative drug-metabolising enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

In a study of 12 female volunteers, lamotrigine did not affect plasma concentrations of ethinyloestradiol and levonorgestrel following the administration of the oral contraceptive pill.

However, as with the introduction of other chronic therapy in patients taking oral contraceptives, any change in the menstrual bleeding pattern should be reported to the patient's physician.

Although changes in the plasma concentrations of other anti-epileptic drugs have been reported, controlled studies have

shown no evidence that lamotrigine affects the plasma concentrations of concomitant anti-epileptic drugs. Evidence from *in vitro* studies indicates that lamotrigine does not displace other anti-epileptic drugs from protein binding sites.

Anti-epileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes enhance the metabolism of lamotrigine.

The pharmacokinetics of lithium after 2g 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 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 drugs 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.

4.6 Pregnancy and lactation

Fertility:
Administration of lamotrigine did not impair fertility in animal reproductive studies.
There is no experience of the effect of lamotrigine on human fertility.

Teratogenicity:
Reproduction toxicology studies with lamotrigine in animals at doses of the human therapeutic dosage showed no teratogenic effects. However, as lamotrigine is a weak inhibitor of dihydrofolate reductase. There is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

Pregnancy:
There are insufficient data available on the use of lamotrigine in human pregnancy to evaluate its safety. As with most drugs, lamotrigine should not be used in pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Lactation:
There is limited information on the use of lamotrigine in lactation.

Preliminary data indicate that it passes into breast milk in concentrations usually of the order of 40-45% of the serum concentration.

In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur.
The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant.

4.7 Effects on ability to drive and use machines

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

In clinical trials with lamotrigine adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how lamotrigine therapy affects +them before driving or operating machinery.

Epilepsy:
As there is individual variation in response to all anti-epileptic drug therapy patients should consult their physician on the specific issues of driving and epilepsy.

4.8 Undesirable effects

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

The following convention has been utilised for the classification of undesirable effects:- Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

EPILEPSY

Skin and subcutaneous tissue disorders

During monotherapy clinical trials:

Very common: Skin rash.

During other clinical experience:

Very common: Skin rash.
Rare: Stevens Johnson Syndrome.
Very rare: Toxic Epidermal Necrolysis.

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 8 weeks of starting treatment and resolves on withdrawal of lamotrigine (see 4.4 *Special Warnings and Special Precautions for Use*).

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 4.4 *Special Warnings and Special Precautions for Use*).

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 4.2 *Posology and Method of Administration*).

- Concomitant use of valproate (see 4.2 *Posology and Method of Administration*).

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

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 (DIC), 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 (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. 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: Irritability.
Uncommon: Aggression.
Very rare: Tics, hallucinations, confusion.

Nervous system disorders

During monotherapy clinical trials:

Very common: Headache.
Common: Drowsiness, insomnia, dizziness, tremor.
Uncommon: Ataxia.

During other clinical experience:

Very common: Headache, dizziness.
Common: Nystagmus, tremor, ataxia, drowsiness, insomnia.
Very rare: Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, chloreoathetosis, 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

Very common: Diplopia, blurred vision.
Rare: Conjunctivitis.

Gastrointestinal disorders

During monotherapy clinical trials:

Common: Nausea.

During other clinical experience:

Common: Gastrointestinal disturbance (including vomiting and diarrhoea).

Hepato-biliary disorders

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

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

Musculoskeletal and connective tissue disorders

Very rare: Lupus-like reactions.

General disorders and administration site conditions

Common: Tiredness.

BIPOLAR DISORDER

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

Skin and subcutaneous tissue disorders

During bipolar disorder clinical trials:

Very common: Skin rash.
Rare: Stevens Johnson Syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 14% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 9% of patients taking lamotrigine and in 8% of patients taking placebo.

Nervous system disorders

During bipolar disorder clinical trials:

Very common: Headache.
Common: Agitation, somnolence, dizziness.

Musculoskeletal and connective tissue disorders

During bipolar disorder clinical trials:

Common: Arthralgia.

General disorders and administration site conditions

During bipolar disorder clinical trials:

Common: Pain, back pain.

4.9 Overdose

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

A patient who ingested a dose calculated to be between 4 and 5g lamotrigine was admitted to hospital with coma lasting 8-12 hours followed by recovery over the next 2 to 3 days. A further patient who ingested 5.6 g lamotrigine was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N03 AX09.

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

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

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

Clinical efficacy in the prevention of depressive episodes in patients with bipolar disorder:

Two pivotal studies have demonstrated efficacy in the prevention of depressive episodes in patients with bipolar I disorder.

Clinical study SCAB20003 was a multi-centre, double-blind, double-dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of five treatment groups: lamotrigine (50, 200, 400 mg/day), lithium (serum levels of 0.8 to 1.1 mEq/L) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)," where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.003 to 0.029. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the lamotrigine patients had longer times to first depressive episode than placebo patients (p=0.047), and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

Clinical study SCAB2006 was a multi-centre, double-blind, double dummy, placebo and lithium-controlled, randomised, flexible dose evaluation of lamotrigine in the long-term prevention of relapse and recurrence of manic and/or depression in patients with bipolar I disorder who had recently or were currently experiencing a manic or hypomanic episode. Once stabilised using lamotrigine monotherapy or lamotrigine plus psychotropic medication, patients were randomly assigned into one of three treatment groups: lamotrigine (100 to 400 mg/day), lithium (serum levels of 0.8 to 1.1 mEq/L) or placebo for a maximum of 76 weeks (18months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)," where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.018 to 0.030. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the

lamotrigine patients had longer times to first depressive episode than placebo patients (p=0.015), and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant. Approximately 30% of the patients included in both pivotal studies were rapid cyclers (≤6 episodes a year).

In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on lamotrigine therapy was not significantly different to placebo.

5.2 Pharmacokinetic properties

Absorption:
Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations 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 drugs metabolised by cytochrome P_{450} 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. In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

The half-life of lamotrigine is greatly affected by concomitant medication.

Mean half-life is reduced to approximately 14 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (see 4.2 *Posology and Method of Administration).*

Children:
Clearance adjusted for bodyweight 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 drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (see 4.2 Posology and Method of Administration).

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 35mL/min at age 20 to 31mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150mg single dose. The mean clearance in the elderly (0.39mL/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.

Patients with renal impairment:
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.

Patients with 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 to 0.34 mL/min /kg in the healthy controls. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

5.3 Preclinical safety data

Mutagenicity:
The results of a wide range of mutagenicity tests indicate that lamotrigine does not present a genetic risk to man.

Carcinogenicity:
Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Povidone
Sodium starch glycollate, Type A
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu blister packs of 10 and 60 tablets.

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

Rowex Ltd
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/96/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2005

10 DATE OF REVISION OF THE TEXT

December 2005