NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Arrow - Lamotrigine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg, 5 mg, 25 mg, 50 mg, 100 mg or 200 mg lamotrigine.

Excipient with known effect: saccharin sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Arrow - Lamotrigine 2 mg: White to off-white, round tablets embossed with 'LI' over '2' on one side and '' on the other side

Arrow - Lamotrigine 5 mg: White to off-white, oval tablet, embossed with 'LI' scoreline '5' on one side and '' on the other side

Arrow - Lamotrigine 25 mg: White to off-white, shield-shaped tablet, embossed with '' over 'LI25' on one side and a scoreline on the other side

Arrow - Lamotrigine 50 mg: White to off-white, shield-shaped tablet, embossed with '' over 'LI50' on one side and a scoreline on the other side

Arrow - Lamotrigine 100 mg: White to off-white, shield-shaped tablet, embossed with '' over 'LI100' on one side and a scoreline on the other side

Arrow - Lamotrigine 200 mg: White to off-white, shield-shaped tablet, embossed with '' over 'LI200' on one side and a scoreline on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Adults and Adolescents (over 12 years of age)

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.

Children (2 to 12 years of age)

Adjunctive therapy in the treatment of epilepsy, for partial seizures and generalised seizures including tonic-clonic seizures and the seizures associated with Lennox-Gaustaut syndrome.

Bipolar Disorder

Adults (18 years of age and over)

Prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

4.2 Dose and method of administration

Dose

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 Special warnings and precautions for use). 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 Pharmacokinetic properties), lamotrigine should generally be escalated to the maintenance dose according to the appropriate schedule.

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

Epilepsy

Epilepsy add-on therapy - Adults and Adolescents (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 to 50 mg every 1 to 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 concomitant AEDs or other medications (see section 4.5 Interaction with other medicines and other forms of interaction) that induce lamotrigine glucuronidation 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 200-400mg/day given in two divided doses.

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

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction), the initial lamotrigine dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Recommended treatment regimen in epilepsy for adults and adolescents over 12 years of age

Treatment regimen	Weeks 1 and 2	Weeks 3 and 4	Maintenance dose
Add-on therapy with valproate, regardless of any concomitant medications	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once daily)	100 to 200 mg/day (once daily or two divided doses) To achieve maintenance, doses may be increased by 25 to 50 mg every 1 to 2 weeks
Add-on therapy without valproate			
This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or	50 mg/day (once daily)	100 mg/day (two divided doses)	200 to 400 mg/day (two divided doses) To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks

- other inducers of lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)			
This regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	25 mg/day (once daily)	50 mg/day (once daily)	100 to 200 mg/day (once daily or two divided doses) To achieve maintenance, doses may be increased by 50 to 100 mg every 1 to 2 weeks
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5 Interaction with other medicines and other forms of interaction), the treatment regimen 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 section 4.4 Special warnings and precautions for use).

Epilepsy add-on therapy – 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 to 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

In those patients taking concomitant AEDs or other medications (see section 4.5 Interaction with other medicines and other forms of interaction) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial lamotrigine dose is 0.6mg/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 once a day or in two divided doses, with a maximum of 400 mg/day.

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction), the initial lamotrigine dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 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.

Recommended treatment regimen in epilepsy for children aged 2-12 years (total daily dose in mg/kg bodyweight/day)**

Treatment regimen	Weeks 1 and 2	Weeks 3 and 4	Maintenance dose
Add-on therapy with valproate, regardless of any concomitant medications	0.15 mg/kg* (once daily)	0.3 mg/kg (once daily)	0.3 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 1 to 5 mg/kg (once daily or two

			divided doses) to a maximum of 200 mg/day
Add-on therapy without valproate			
This regimen should be used with: - phenytoin - carbamazepine - phenobarbitone - primidone or - other inducers of lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	1.2 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 5 to 15 mg/kg (once daily or two divided doses) to a maximum of 400 mg/day
This regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every 1 to 2 weeks to achieve a maintenance dose of 1 to 10 mg/kg (once daily or two divided doses) to a maximum of 200 mg/day
NOTES: (1) In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5 Interactions with other medicines and other forms of interaction), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used. *(2) If the calculated daily dose in patients taking valproate is 1 to 2 mg, then 2 mg lamotrigine may be taken on alternate days for the first 2 weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered. DO NOT attempt to give partial quantities of the dispersible/chewable tablets.			

** If the calculated dose of lamotrigine cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet.

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section 4.4 Special warnings and 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.

Epilepsy add-on therapy - Children aged less than 2 years

Lamotrigine has not been studied as monotherapy in children less than 2 years of age or as add-on therapy in children less than 1 month of age. The safety and efficacy of lamotrigine as add-on therapy of partial seizures in children aged 1 month to 2 years has not been established (see 5.1 Pharmacodynamic properties). Therefore lamotrigine is not recommended in children less than 2 years of age.

General Dosing Recommendations for Epilepsy

When other anti-epileptic drugs (AEDs) are added-on to treatment regimens containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5 Interaction with other medicines and other forms of interaction).

Bipolar Disorder - Adults (18 years of age and over)

Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section 4.4 Special warnings and precautions for use).

Lamotrigine is recommended for use in bipolar patients at risk for a future depressive episode.

The following transition regimen should be followed to prevent recurrence of depressive episodes. The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks after which other psychotropic and/or anti-epileptic drugs can be withdrawn, if clinically indicated.

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with lamotrigine in mania has not been conclusively established.

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 and 2**	**Weeks 3 and 4**	**Week 5**	**Target stabilisation dose (week) 6****
a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once daily)	50 mg/day (once daily or two divided doses)	100 mg/day (once a day or two divided doses) (maximum 200 mg daily)
b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	50 mg/day (once daily)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6 If necessary, increasing to 400 mg/day in week 7 (two divided doses)
c) Adjunct therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction) or **Monotherapy with lamotrigine**	25 mg/day (once daily)	50 mg/day (once daily or two divided doses)	100 mg/day (once daily or two divided doses)	200 mg/day (range 100 to 400 mg) (once daily or two divided doses)
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5 Interactions with other medicines and other forms of interaction), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.				

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

a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. Valproate.

In patients taking glucuronidation 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 100mg/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.

b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as Valproate. This dosage regiment should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction).

In those patients currently taking drugs that induce lamotrigine glucuronidation and NOT taking valproate, the initial lamotrigine dose is 50 mg once a day for two weeks, followed by 100mg/day given in two divided doses for two weeks. The dose should be increased to 200mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day 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.

c) Adjunct therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction).

The initial lamotrigine dose 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 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 to 400 mg was used in clinical trials.

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule below.

Maintenance stabilisation total daily dose in bipolar disorder following withdrawal of concomitant psychotropic or anti-epileptic drugs

Treatment regimen	Week 1	Week 2	Week 3 onwards*
a) Following withdrawal of inhibitors of lamotrigine glucuronidation 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	200 mg/day (two divided doses)	200 mg/day (two divided doses)
b) Following withdrawal of inducers of lamotrigine glucuronidation, depending on original dose This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	400 mg/day	300 mg/day	200 mg/day
	300 mg/day	225 mg/day	150 mg/day
	200 mg/day	150 mg/day	100 mg/day
c) Following withdrawal of other drugs that do not significantly inhibit or induce lamotrigine glucuronidation	Maintain target dose achieved in dose escalation (i.e. 200 mg/day in two divided doses; range 100 to 400mg)		

(see section 4.5 Interaction with other medicines and other forms of interaction)	
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen recommended for lamotrigine is to initially maintain the current dose and adjust the lamotrigine treatment based on clinical response.	

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

(a) Following withdrawal of adjunct therapy with inhibitors of lamotrigine glucuronidation 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.

(b) Following withdrawal of adjunct therapy with inducers of lamotrigine glucuronidation, depending on original maintenance dose. This regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone or other drugs known to induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction).

The dose of lamotrigine should be gradually reduced over 3 weeks as the glucuronidation inducer is withdrawn.

(c) Following withdrawal of adjunct therapy with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction).

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

Adjustment of lamotrigine daily dosing in patients with bipolar disorder following addition of other medications

There is no clinical experience in adjusting the lamotrigine daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made:

Adjustment of lamotrigine daily dosing in patients with bipolar disorder following the addition of other medications

Treatment regimen	Current lamotrigine stabilisation dose	Week 1	Week 2	Week 3 onwards
Addition of inhibitors of lamotrigine glucuronidation e.g. valproate, depending on original dose of lamotrigine	200 mg/day	100 mg/day	100 mg/day	100 mg/day
	300 mg/day	150 mg/day	150 mg/day	150 mg/day
	400 mg/day	200 mg/day	200 mg/day	200 mg/day
Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate and depending on original dose of lamotrigine This regimen should be used with: - phenytoin; - carbamazepine; - phenobarbitone; - primidone; or - other inducers of lamotrigine glucuronidation (see section 4.5	200 mg/day	200 mg/day	300 mg/day	400 mg/day
	150 mg/day	150 mg/day	225 mg/day	300 mg/day
	100 mg/day	100 mg/day	150 mg/day	200 mg/day

Interaction with other medicines and other forms of interaction)				
Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 Interaction with other medicines and other forms of interaction)	Maintain target dose achieved in dose escalation (i.e. 200 mg/day; range 100 to 400 mg)			
NOTE: In patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5 Interaction with other medicines and other forms of interaction), the treatment regimen 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.

Bipolar Disorder - Children and Adolescents (less than 18 years of age)
Lamotrigine is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (see section 4.4 Special warnings and precautions for use). Safety and efficacy of lamotrigine in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

General Dosing Recommendations for lamotrigine in special patient populations
Women taking hormonal contraceptives
(a) Starting lamotrigine in patients already taking hormonal contraceptives:

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see section 4.4 Special warnings and precautions for use), no adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether lamotrigine is added to valproate (an inhibitor of lamotrigine glucuronidation) or to an inducer of lamotrigine glucuronidation, or whether lamotrigine is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

(b) 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 section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicines and other forms of interaction). 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.

(c) 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 section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicines and other forms of interaction). It is recommended to gradually decrease the daily dose of lamotrigine by 50 to 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.

Use with other oestrogen-containing products
Other oestrogen-containing therapies, such as hormone replacement therapies (HRTs), may interfere with lamotrigine. Therefore, close clinical monitoring on effectiveness of lamotrigine with dose adjustment may be necessary (see section 4.4 Special warnings and precautions for use).

Use with atazanavir/ritonavir
Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (see section 4.5 Interaction with other medicines and other forms of interaction – interactions involving other medications), no adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether lamotrigine is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether lamotrigine is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued.

Special populations
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 section 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' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (see section 4.4 Special warnings and precautions for use). For more detailed pharmacokinetic information see section 5.2 Pharmacokinetic properties.

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

DO NOT attempt to administer partial quantities of the dispersible/chewable tablets. 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.

4.3 Contraindications
Lamotrigine is contraindicated in individuals with known hypersensitivity to lamotrigine or any other ingredient of the preparation.

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 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 such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 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 section 4.2 Dose and method of administration).
- Concomitant use of valproate, (see section 4.2 Dose and method of administration).

Caution is also required when treating patients with a history of allergy or rash to other anti-epileptic drugs 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.

Limited data suggest that human leukocyte antigen (HLA)-B*1502 allele in individuals of Asian (primarily Han Chinese and Thai) origin is associated with the risk of developing SJS/TEN when treated with lamotrigine. However, there are patients who are positive for HLA-B*1502 who do not go on to develop SJS/TEN, and SJS/TEN may still occur in patients taking lamotrigine who are found to be negative for HLA- B*1502. If patients are known to be carrying this genetic variant, the benefits of treatment with lamotrigine should be carefully weighed against the risk of developing SJS/TEN.

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. 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney and aseptic meningitis (see section 4.8 Undesirable effects). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ 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.

Aseptic meningitis
Post-marketing cases of aseptic meningitis have been reported in paediatric and adult patients taking lamotrigine for various indications. Aseptic meningitis was reversible on withdrawal of the drug in most

cases, but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Haemophagocytic lymphohistiocytosis (HLH)
HLH has occurred in patients taking lamotrigine (see section 4.8). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established.

Suicide risk
Symptoms of depression and/or bipolar disorder may occur in patients with epilepsy, and there is evidence that patients with epilepsy and bipolar disorder have an elevated risk for suicidality.

Twenty-five to 50% of patients with bipolar disorder attempt suicide at least once, and may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including lamotrigine.

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEDs (including lamotrigine) 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. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Worsening of seizure frequency
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.

Clinical worsening in bipolar disorder
Patients receiving lamotrigine for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Effects of oestrogen-containing products including hormonal contraceptives on lamotrigine efficacy

An ethinylestradiol/levonorgestrel (30 micrograms/150 micrograms) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5 Interaction with other medicines and other forms of interaction). 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. In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive medication. For dosing instructions see section 4.2 Dose and method of administration, General dosing recommendations for lamotrigine in special populations – Women taking hormonal contraceptives.

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during lamotrigine therapy and lamotrigine dosing adjustments will be needed in most cases.

Other oral contraceptive and other oestrogen-containing therapies (such as HRT) treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see section 4.2 Dose and method of administration, General Dosing Recommendations for lamotrigine in special patient populations (for dosing instructions for women taking hormonal contraceptives) and section 4.4 Special warnings and precautions for use).

Effects of lamotrigine on hormonal contraceptive efficacy

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinylestradiol/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 Interaction with other medicines and other forms of interaction). 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.

Effect of lamotrigine on organic cationic transporter 2 (OCT 2) substrates

Lamotrigine is an inhibitor of renal tubular secretion via OCT 2 proteins (see section 4.5 Interaction with other medicines and other forms of interaction). This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Co- administration of lamotrigine with OCT 2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

Dihydrofolate reductase

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.

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.

Brugada-type ECG
A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using lamotrigine in patients with Brugada syndrome.

Cardiac rhythm and conduction abnormalities
In vitro testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these *in vitro* findings, lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia in patients with clinically important structural or functional heart disease. Therefore, any expected or observed benefit of lamotrigine for those patients must be carefully weighed against the potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia (see section 5.1 Pharmacodynamics).

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, multi-organ dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of lamotrigine.

Use in children and adolescents
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents (less than 18 years of age) with major depressive disorder and other psychiatric disorders.

4.5 Interaction with other medicines and other forms of interaction

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Those drugs that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in the table below. Specific dosing guidance for these drugs is provided in section 4.2 Dose and method of administration. In addition, this table lists those drugs which have been shown to have little or no effect on the concentration of lamotrigine. Coadministration of such drugs would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Table of effects of drugs on the concentration of lamotrigine:

Drugs that increase the concentration of lamotrigine	Drugs that decrease the concentration of lamotrigine	Drugs that have little or no effect on the concentration of lamotrigine

Valproate	Carbamazepine Phenytoin Primidone Phenobarbitone Rifampicin Lopinavir/ritonavir Atazanavir/ritonavir Ethinyloestradiol/ levonorgestrel combination	Lithium Bupropion Olanzapine Oxcarbazepine Felbamate Gabapentin Levetiracetam Pregabalin Topiramate Zonisamide Aripiprazole Lacosaminde Perampanel

For dosing guidance, see section 4.2 Dose and method of administration - General Dosing Recommendations for Lamotrigine in Special Patient Populations, plus for women taking hormonal contraceptives also see section 4.4 Special warnings and precautions for use – Effects of oestrogen-containing products including hormonal contraceptives on lamotrigine efficacy and Effects of lamotrigine on hormonal contraceptive efficacy.

Interactions involving AEDs (see section 4.2 Dose and method of administration)
Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain anti-epileptic agents (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine.

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 IR and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

In a 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.

In a study of healthy volunteers, co-administration 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 drug 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, co-administration 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.

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400 or 400 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10%.

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.

Interactions involving other psychoactive agents (see section 4.2 Dose and method of administration)
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.

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 Cmax of lamotrigine by an average of 24% and 20%, respectively. 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 a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (>/=100 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for a further 7 days. An average reduction of approximately 10% in Cmax and AUC of lamotrigine was observed.

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, fluoxetine, 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, phenelzine, risperidone, sertraline or trazodone.

Interactions involving hormonal contraceptives
Effect of hormonal contraceptives on lamotrigine pharmacokinetics
In a study of 16 female volunteers, 30 micrograms ethinylestradiol/150 micrograms levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and Cmax, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy (see section 4.2 Dose and method of administration – General Dosing Recommendations for lamotrigine in special

patient populations (for dosing instructions for women taking oestrogen-containing products including hormonal contraceptives) and section 4.4 Special warnings and precautions for use – Effects of oestrogen-containing products including hormonal contraceptives on lamotrigine efficacy and Effects of lamotrigine on hormonal contraceptive efficacy).

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 ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and Cmax, respectively. Measurement of serum FSH, LH and estradiol 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 Special warnings and precautions for use).

The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations (including progesterone/progesterone containing HRT) have not been conducted.

Interactions involving other medications
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 treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (see section 4.2 Dose and method of administration).

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 treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (see section 4.2 Dose and method of administration).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and Cmax of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively (see section 4.2 Dose and method of administration – General Dosing Recommendations for Lamotrigine in Special Patient Populations).

In a study in healthy adult volunteers, paracetamol 1g (four times daily) reduced the plasma AUC and C_{min} of lamotrigine by an average of 20% and 25%, respectively.

General Dosing Recommendations for Lamotrigine in Special Patient Populations
Data from in vitro assessment of the effect of lamotrigine at OCT 2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT 2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with IC50 value of 53.8 μM (see section 4.4 Special warnings and precautions for use).

Laboratory tests
Lamotrigine has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for phencyclidine (PCP). A more specific alternative chemical method should be used to confirm a positive result.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category D)

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.

Postmarketing data from several prospective pregnancy registries have documented outcomes in over 8,700 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations. Although data from a limited number of registries have reported an increase in the risk of isolated oral cleft malformations, a completed case control study did not demonstrate an increased risk of oral clefts compared to other major congenital malformations following exposure to lamotrigine (see section 5.3 Preclinical safety data).

The data on use of lamotrigine in polytherapy combinations are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant lamotrigine use.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during lamotrigine therapy should be ensured.

Use in lactation

Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother's. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

The potential benefits of breast feeding should be weighed against the potential risk of adverse effects occurring in the infant.

Fertility

Administration of lamotrigine did not impair fertility in animal reproductive studies.

There is no experience of the effect of lamotrigine on human fertility.

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.

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 adverse reactions identified from epilepsy or bipolar disorder clinical trial data have been divided into indication specific sections. Additional adverse reactions identified through post-marketing surveillance for both indications are included in the post-marketing section. All three 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 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10,000 to <1/1000); very rare (<1/10,000).

Epilepsy

The following adverse reactions were identified during epilepsy clinical trials and should be considered alongside those seen in the bipolar disorder clinical trials and post-marketing sections for an overall safety profile of lamotrigine.

Skin and subcutaneous tissue disorders
Very common: Skin rash.
Rare: Erythema multiforme, Stevens-Johnson Syndrome.
Very rare: Toxic epidermal necrolysis.

In double-blind, add-on 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 8 weeks of starting treatment and resolves on withdrawal of lamotrigine (see section 4.4 Special warnings and precautions for use).

Rarely, 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 drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4 Special warnings and 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 section 4.2 Dose and method of administration).
- Concomitant use of valproate (see section 4.2 Dose and method of administration).

Rash has also been reported as part of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms (see section 4.4 Special warnings and precautions for use and Immune system disorders**).

Blood and lymphatic system disorders
Very rare: Haematological abnormalities (including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis), lymphadenopathy.

Haematological abnormalities and lymphadenopathy may or may not be associated with DRESS/Hypersensitivity syndrome (see Section 4.4 Special warnings and precautions for use and Immune system disorders**).

Immune system disorders
Very rare: DRESS/Hypersensitivity syndrome** including such symptoms as fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney.

**Rash has also been reported as part of this syndrome which shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ 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: Aggression, irritability.
Very rare: Tics, hallucinations, confusion.

Anti-epileptic medicines have been associated with an increased risk of suicidal behaviour, suicidal ideation and emergence or worsening of existing depression.

Nervous system disorders
Very common: Headache.
Common: Somnolence, dizziness, tremor, insomnia.
Rare: Ataxia
Very rare: Nystagmus

Eye disorders
Uncommon: Diplopia, blurred vision.

Gastrointestinal disorders
Very common: Nausea, vomiting, diarrhoea.

Hepatobiliary 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 following adverse reactions were identified during bipolar disorder clinical trials and should be considered alongside those seen in epilepsy clinical trials and post-marketing sections for an overall safety profile of lamotrigine.

Skin and subcutaneous tissue disorders
Very Common: Skin rash.
Rare: Erythema multiforme, Stevens-Johnson Syndrome.

When all bipolar disorder studies (controlled and uncontrolled) conducted with lamotrigine are considered, skin rashes occurred in 12% of patients on lamotrigine. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking lamotrigine and in 6% of patients taking placebo.

Nervous system disorders
Very Common: Headache.
Common: Agitation, somnolence, dizziness.

Musculoskeletal and connective tissue disorders
Common: Arthralgia.

General disorders and administration site conditions
Common: Pain, back pain.

Post-marketing
This section includes adverse reactions identified through post-marketing surveillance for both indications. These adverse reactions should be considered alongside those seen in the epilepsy and bipolar disorder clinical trials sections for an overall safety profile of lamotrigine.

Blood and lymphatic system disorders
Very rare: Haemophagocytic lymphohistiocytosis (see section 4.4 Special warnings and precautions for use), pseudolymphoma

Immune system disorders
Very rare: Hypogammaglobulinaemia

Skin and subcutaneous tissue disorders
Rare: Alopecia

Uncommon: Photosensitivity reaction

Psychiatric disorders
Very rare: Nightmares

Nervous system disorders
Very common: Somnolence, ataxia, headache, dizziness.
Common: Nystagmus, tremor, insomnia.

Rare: Aseptic meningitis (see section 4.4 Special warnings and precautions for use), 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
Rare: Conjunctivitis.

Renal and urinary disorders
Very rare: Tubulointerstitial nephritis*
* may occur in association with uveitis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

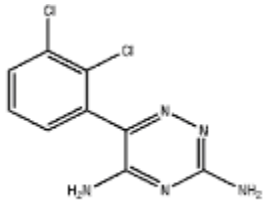
4.9 Overdose
Symptoms and signs
Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose of Lamotrigine, have been reported, including fatal cases. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has also been observed in overdose patients.

Treatment
In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy as clinically indicated or as recommended by the national poisons centre, where available.

For risk management and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiepileptics; other antiepileptics, ATC code: N03AX09

Lamotrigine is a white to pale cream coloured powder, slightly soluble in ethanol and chloroform and very slightly soluble in water. The chemical name of lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Its structural formula is:



$C_9H_7Cl_2N_5$ Molecular weight: 256.09 CAS: 84057-84-1

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.

In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia.

In tests designed to evaluate the central nervous system effects of medicines, 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 coordination 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

Adjunctive therapy in patients aged 1–24 months with partial seizures

The effectiveness of lamotrigine as adjunctive therapy in patients aged 1 to 24 months with partial seizures was evaluated in a multi-centre, double-blind, placebo-controlled add-on trial. Lamotrigine was added to 1 or 2 AEDs during an open-label phase (n=177).

Lamotrigine was given on alternate days or once daily if an initial total dose or dose-titration step of less than 2 mg was required. 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 ug/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. If valproate was used as an AED, lamotrigine was added only after an infant had been on valproate for 6 months without liver function test abnormalities. The safety and efficacy of lamotrigine in patients weighing less than 6.7 kg, and taking valproate or AEDs other than carbamazepine, phenytoin, phenobarbital, or primidone has not been evaluated.

Patients achieving a 40% or greater reduction in partial seizure frequency (n=38) were randomised to either gradual withdrawal to placebo (n=19) or continued lamotrigine (n=19) for up to 8 weeks. The primary efficacy endpoint was based on the difference in the proportion of subjects receiving lamotrigine or placebo who met defined escape criteria. The escape criteria allowed the withdrawal of subjects from the study if their epilepsy conditions showed any signs of clinical deterioration. Statistical

significance on the primary endpoint was not achieved; however, fewer patients met escape criteria on lamotrigine (58%) compared with placebo (84%) and took a longer time to meet escape criteria (42 versus 22 days).

The adverse event profile was similar to that seen in older children.

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 (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 0.023. 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.

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 450mg, 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 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. 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 glucuronidation-inducing drugs 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 Dose and method of administration and section 4.5 Interaction with other medicines and other forms of interaction).

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 section 4.2 Dose 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 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. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150mg 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 9 studies with non-elderly adults after single doses of 30 to 450 mg.

Patients with renal impairment
Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were each given a single 100mg dose of lamotrigine. Mean CL/F 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 to 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 to 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 patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment.

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.

Teratogenicity
Reproductive toxicology studies with lamotrigine in animals at doses less than the human dose of 400 mg/day [on a body surface area (mg/m2) basis] showed developmental toxicity (increased mortality, decreased body weight, increased structural variations, neurobehavioral abnormalities), but 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, povidone, saccharin sodium, purified talc, magnesium stearate and blackcurrant flavour.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 25°C; protect from light and moisture.

6.5 Nature and contents of container
PVC/PVdC/Aluminium foil blister strips.

2 mg & 5 mg: Pack sizes of 30 tablets.

2 mg, 5 mg, 25 mg, 50 mg, 100 mg & 200 mg: Pack sizes of 56 tablets.

Not all strengths or pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

6 July 2006

10. DATE OF REVISION OF THE TEXT

06 June 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of HLA-B*1502 allele and risk of Serious Cutaneous Adverse Reactions (SCARs) as a warning and precaution. Replace hormone replacement therapy with 'other oestrogen-containing therapies (such as HRT)
4.8	Addition of photosensitivity reaction
4.9	Added risk assessment wording