AUSTRALIAN PRODUCT INFORMATION

LOGEM®

(lamotrigine) chewable/dispersible tablet

Severe, potentially life-threatening rashes have been reported in association with the use of lamotrigine, particularly in children. Accordingly, lamotrigine should be discontinued at the first sign of rash unless the rash is clearly not drug related (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

1 NAME OF THE MEDICINE

Lamotrigine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable/dispersible tablet contains lamotrigine as the active ingredient. Each LOGEM chewable/dispersible tablet contains either 25 mg, 50 mg, 100 mg or 200 mg of the active ingredient.

Excipients of known effect: saccharin and sulfites

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LOGEM chewable/dispersible tablets have a blackcurrant odour.

LOGEM 25 mg tablets are white to off-white, round, flat faced, bevelled edge tablets with "LY" over "25" on one side and plain on the other side.

LOGEM 50 mg tablets are white to off-white, round, flat faced, bevelled edge tablets with "LY" over "50" on one side and plain on the other side.

LOGEM 100 mg tablets are white to off-white, round, flat faced, bevelled edge tablets with "LY" over "100" on one side and plain on the other side.

LOGEM 200 mg tablets are white to off-white, round, flat faced, bevelled edge tablets with "LY" over "200" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lamotrigine is an anti-epileptic drug used for the treatment of partial and generalised seizures in adults and children.

There is extensive experience with lamotrigine used initially as add-on therapy. Lamotrigine has also been found to be effective as monotherapy following withdrawal of concomitant anti-epileptic drugs.

Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended (see section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

It is strongly recommended that therapy with LOGEM is initiated at the recommended doses. Careful incremental titration of the dose may decrease the severity of skin rashes.

If a calculated dose of lamotrigine (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets. If the calculated dose is 1-2 mg, 2 mg lamotrigine may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg then lamotrigine should not be administered (see Add-on Therapy in Children aged 2 to 12 years).

Since the minimum strength available for LOGEM is the 25 mg tablet, other lamotrigine products with 2 mg and 5 mg strengths should be used instead of LOGEM if the calculated dose is less than 25 mg.

When concomitant antiepileptic drugs are withdrawn to achieve LOGEM monotherapy or other anti-epileptic drugs (AEDs) are added-on to treatment regimens containing LOGEM, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Monotherapy in Adults and Children 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 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 (see Table 1).

Add-on Therapy in Adults and Children Over 12 Years of Age

In those patients taking sodium valproate, the initial LOGEM 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 one to two weeks until optimal response is achieved. The usual maintenance dose is 100 to 200 mg/day given once a day or as a divided dose (see Table 1).

The initial LOGEM dose in those patients not taking sodium valproate 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 one to two weeks until the optimal response is achieved. The usual maintenance dose is 200 to 400 mg/day given as a divided dose (see Table 1).

In open continuation studies, some patients were safely maintained on doses of lamotrigine in the range 500 to 700 mg daily for periods of up to approximately one year at the time of study completion.

In those patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), 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 an optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Table 1: Recommended Treatment Regimen in EPILEPSY for Adults and Children Over 12 Years of Age

Treatment Regimen		**Weeks 1 - 2**	**Weeks 3 - 4**	**Maintenance Dose**
Monotherapy		25 mg (once a day)	50 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks.
Add-on therapy with valproate regardless of any concomitant medications		12.5 mg (given 25 mg alternate days)	25 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25 – 50 mg every one to two weeks.
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbital (phenobarbitone) Primidone Or with other inducers of lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).	50 mg (once a day)	100 mg (two divided doses)	200 – 400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every one to two weeks.
	This dosage should be taken with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)	25 mg (once a day)	50 mg (once a day)	100 – 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 – 100 mg every one to two weeks.
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 INTERACTIONS), 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).

Add-on Therapy in Children Aged 2 to 12 Years

In patients taking sodium 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 bodyweight/day given once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every 1-2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1-5 mg/kg bodyweight/day given once a day or as a divided dose, with a maximum of 200 mg/day (see Table 2).

In those patients taking concomitant AEDs or other medications (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) that induce lamotrigine glucuronidation with/without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given as a divided dose for two weeks, followed by 1.2 mg/kg bodyweight/day for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every 1 to 2 weeks until optimal response is achieved. The usual maintenance dose is 5 to 15 mg/kg bodyweight/day given as a divided dose, with a maximum of 400 mg/day (see Table 2).

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), 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.

Table 2: Recommended Treatment Regimen in EPILEPSY for Children Aged 2 to 12 Years (total daily dose in mg/kg bodyweight/day)

Treatment regimen		**Weeks 1 - 2**	**Weeks 3 - 4**	**Maintenance Dose**
Add-on therapy with valproate regardless of any other concomitant medication		0.15 mg/kg* (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbital (phenobarbitone) Primidone Or with other inducers of lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 – 15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.

	This dosage should be taken with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 – 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.				
*(Where 2 mg tablets are the lowest marketed strength) NOTE: 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 two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then lamotrigine should not be administered.				

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see section 4.4 SPECIAL WARINGS AND PRECAUTIONS FOR USE).

It is likely that patients aged less than 6 years will require a maintenance dose at the higher end of the recommended range.

Children (less than 2 years of age)

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 (trial data shows plasma concentrations may be unexpectedly high in some patients in this age group). Therefore, lamotrigine is not recommended in children less than 2 years of age.

General Dosing Considerations for Add-on Therapy

For patients receiving LOGEM in combination with other anti-epileptic drugs, whether or not optimal dosing has been achieved, a re-evaluation of all anti-epileptic drugs in the regimen should be considered if a change or no improvement in seizure control or an appearance or worsening of adverse experiences is observed (see section 4.4 SPECIAL WARINGS AND PRECAUTIONS FOR USE).

Withdrawal of Concomitant Antiepileptic Drugs

The dose of LOGEM following the withdrawal of concomitant anti-epileptic drugs will be dependent upon the pharmacokinetics of the drugs(s) being withdrawn, together with the overall clinical response of the patient. The withdrawal of enzyme inducing anti-epileptic drugs (e.g. phenytoin and carbamazepine) may not require a reduction in the lamotrigine dose unless there is a need due to safety considerations. An increase in the lamotrigine dose may, however, be required following the withdrawal of enzyme inhibiting anti-epileptic drugs (e.g. sodium valproate) (see section 4.4 SPECIAL WARINGS AND PRECAUTIONS FOR USEand section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Discontinuation of Lamotrigine in Patients with Epilepsy

As with other anti-epileptic drugs, abrupt withdrawal of lamotrigine may provoke rebound seizures and should be avoided wherever possible. Unless safety concerns (for example serious skin reactions) require an abrupt withdrawal, the dose of lamotrigine should be gradually decreased over a period of two weeks.

General Dosing Recommendations in Special Patient Populations

Women Taking Hormonal Contraceptives

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 WARINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), 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 enzyme inhibitor of lamotrigine glucuronidation) or to an enzyme inducer of lamotrigine glucuronidation, or whether lamotrigine is added in the absence of valproate or an inducer of lamotrigine glucuronidation (see Table 1 for epilepsy).

Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking enzyme 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 WARINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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.

Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking enzyme 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 WARINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 Atazanavir/Ritonavir

Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS), 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.

The Elderly

To date, there is no evidence to suggest that the response of this age group differs from that in young patients with epilepsy. The dosage schedule recommended in adults and children greater than 12 years of age, can be applied to the elderly population (aged 65 years or more). As older patients are more likely to suffer from intercurrent illness and require medications to treat other medical conditions, LOGEM should be used cautiously in these patients and they should be monitored regularly.

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 accordingly to clinical response.

Renal Impairment

Caution should be exercised when administering lamotrigine to patients with renal failure. For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment.

Administration

All LOGEM tablets, which have been formulated as dispersible/chewable tablets, may be swallowed whole, chewed or dispersed in a small volume of water (at least enough to cover the whole tablet).

4.3 CONTRAINDICATIONS

LOGEM is contraindicated in individuals with known hypersensitivity to lamotrigine or to any other ingredient in LOGEM tablets (see section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Skin Rash

SEE BOXED WARNING REGARDING THE RISK OF SEVERE, POTENTIALLY LIFE-THREATENING RASH ASSOCIATED WITH THE USE OF LOGEM.

There have been reports of adverse skin reactions, which have generally occurred within the first 8 weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however, serious rashes requiring hospitalisation and discontinuation of lamotrigine have been reported. These have included potentially life-threatening skin rashes including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4 SPECIAL WARINGS AND PRECAUTIONS FOR USE and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Although benign rashes also occur with lamotrigine, it is not possible to predict reliably which rashes will prove to be life-threatening.

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).

The risk of serious skin rashes is higher in children 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, which increases the mean half-life of lamotrigine nearly two-fold (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 antiepileptic 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.

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. If the patient has developed SJS, TEN or DRESS with the use of lamotrigine, treatment with lamotrigine must not be restarted in this patient at any time.

There have also been reports of photosensitivity reactions associated with lamotrigine use (see Section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS). If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

Hypersensitivity Syndrome

Rash has also been reported as part of a hypersensitivity syndrome, also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood and liver and aseptic meningitis (see also 'Aseptic meningitis' below). Eosinophilia is often present. Some reports have been fatal or life-threatening. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multi-organ failure. Very rarely, rhabdomyolysis has been observed in patients experiencing severe hypersensitivity reactions, however, it is not possible to determine whether rhabdomyolysis occurred as part of the initial hypersensitivity reaction or if it was a consequence of the clinical complexity of the cases. **It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. Patients should be warned to seek immediate medical advice if signs and symptoms develop. If such signs and symptoms are present, the patient should be evaluated immediately, and lamotrigine discontinued if an alternative aetiology cannot be established.**

Aseptic meningitis

Therapy with LOGEM increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate.

Postmarketing cases of aseptic meningitis have been reported in paediatric and adult patients taking LOGEM for various indications. Symptoms upon presentation have included headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia, myalgia, chills, altered consciousness and somnolence. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment.

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. Some of the patients treated with LOGEM who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.

Cardiac Rhythm and Conduction Abnormalities

In vitro testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Based on this activity, lamotrigine could slow ventricular conduction (widen QRS) and induce proarrhythmia, including sudden death, in people with structural heart disease, myocardial ischemia or multiple risk factors for coronary artery disease. Therefore, avoid the use of LOGEM in people who have cardiac conduction disorders (e.g., second- or third-degree heart block), ventricular arrhythmias, or cardiac disease or abnormality (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome or other sodium channelopathies). Concomitant use of other sodium channel blockers may increase the risk of proarrhythmia.

Haemophagocytic Lymphohistiocytosis

There have been reports of Haemophagocytic lymphohistiocytosis (HLH) with use of lamotrigine in paediatric and adult patients. HLH is an aggressive and life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. It is associated with high

mortality rates if not recognised early and treated. Most patients with HLH are acutely ill with multiorgan involvement. Common findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin and liver function and coagulation abnormalities. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific and thus it may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/hypersensitivity syndrome. All patients who develop fever or rash and/or early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. Lamotrigine should be discontinued if HLH is suspected and an alternative aetiology for the signs and symptoms cannot be established.

Prior to initiation of treatment with lamotrigine, patients should be informed that excessive immune activation may occur with lamotrigine and they should be advised to seek immediate medical attention if they experience symptoms of HLH (such as fever, rash or lymphadenopathy) during lamotrigine treatment.

Abrupt Withdrawal

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

When concomitant AEDs are withdrawn to achieve lamotrigine monotherapy or other AEDs are added-on to lamotrigine monotherapy, considerations should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Suicidal Behaviour and Ideation

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.

Antiepileptic drugs, including lamotrigine, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3: Risk by Indication for Anti-epileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events / 1000 Patients	Drug Patients with Events / 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing lamotrigine, or any other AED, must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Hormonal Contraceptives

Effects of 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 in Special Patient Populations.

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 hormone replacement therapy (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 in Special Patient Populations, for dosing instructions for women taking hormonal contraceptives).

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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 up to 5 years.

Patients Taking Other Lamotrigine Containing Preparations

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 following lamotrigine use. Therefore, careful consideration should be given before using lamotrigine in patients with Brugada syndrome.

Use in Hepatic Impairment

As Lamotrigine is cleared primarily by metabolism in the liver, lamotrigine should be administered with caution in patients with hepatic impairment as clearance is reduced (see section 4.2 DOSE AND METHOD OF ADMINISTRATION – Hepatic Impairment).

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

Use in Renal Impairment

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

Use in the Elderly

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION ; section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Skin Rash and section 5.1 PHARMADYNAMIC PROPERTIES – Clinical Trials.

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Uridine 5'-diphospho (UDP) -glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucoronidation may, therefore, affect the apparent clearance of lamotrigine.

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

Effects of Other Drugs on Glucuronidation of Lamotrigine (see section 4.2 DOSE AND METHOD OF ADMINISTRATION):

Drugs that significantly inhibit glucuronidation of lamotrigine	Drugs that significantly induce glucuronidation of lamotrigine	Drugs that do not significantly inhibit or induce glucuronidation of lamotrigine
Valproate	Carbamazepine Phenytoin Primidone Phenobarbital (phenobarbitone) Rifampicin Lopinavir/ritonavir Atazanavir/ritonavir* Ethinylestradiol/ levonorgestrel combination**	Lithium*** Bupropion Olanzapine Oxcarbazepine Felbamate Gabapentin Levetiracetam Pregabalin Topiramate Zonisamide Aripiprazole

* For dosing guidance, see section 4.2 DOSE AND METHOD OF ADMINISTRATION – General Dosing Recommendations in Special Patient Populations.
** Other oral contraceptive and 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 in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives) and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hormonal Contraceptives.
*** Lithium is unlikely to inhibit or induce glucuronidation of lamotrigine.

Approximately 96% of a given dose of lamotrigine is eliminated by conjugation metabolism mediated by glucuronyl-transferases. Cytochrome P450 is not involved in the elimination of lamotrigine to any significant extent. Therefore, the likelihood that lamotrigine inhibits the elimination of drugs metabolised by cytochrome P450 is low.

Interactions Involving AEDs

Certain antiepileptic drugs (e.g. phenytoin, carbamazepine, phenobarbital (phenobarbitone) and primidone) that induce hepatic drug-metabolising enzymes induce the metabolism glucuronidation of lamotrigine and enhance the metabolism of lamotrigine (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). Other drug classes that induce hepatic drug metabolising enzymes may also enhance the metabolism of lamotrigine.

Sodium valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of lamotrigine. These events usually resolve

when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

In a steady-state pharmacokinetic interaction study in healthy adult volunteers using daily 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. However, the incidence of adverse effects was higher during combination therapy (90%) than during lamotrigine and placebo (48%). Adverse effects were predominantly related to the central nervous system or gastrointestinal tract, including dizziness, headache and nausea.

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.

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. Increases in serum concentrations of zonisamide, leading to symptoms and signs of zonisamide toxicity, have been reported when lamotrigine was added to previously stable zonisamide therapy.

Increases in the plasma concentrations of other anti-epileptic drugs have been reported in a few patients, however 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

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

In a steady-state pharmacokinetic interaction study in healthy adult volunteers, daily doses of 15 mg olanzapine reduced the AUC and C_{max} of 200 mg lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200 mg daily dose 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. However, 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 clinical trials of patients who took risperidone with lamotrigine or placebo, 4 out of 53 patients (7.5%) who received lamotrigine and risperidone reported the occurrence of somnolence or sedation, compared to 2 out of 62 patients (3.2%) who had taken placebo and risperidone.

In 16 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. 15 subjects completed the study at the target dose of 30 mg/day. An average reduction of approximately 10% in C_{max} and AUC of lamotrigine was observed. An effect of this magnitude is not expected to be of clinical consequence.

In vitro experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was inhibited by co-incubation with sodium valproate, bupropion, clonazepam, amitriptyline, haloperidol, and lorazepam. Sodium valproate is known to reduce the clearance of lamotrigine *in vivo* (see above). In these experiments, the largest effect (after that of sodium valproate) was observed with bupropion; however, multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of a low dose (100 mg) of lamotrigine in 12 subjects and caused only a slight increase in the AUC of lamotrigine glucuronide. This observation suggests that the risk of a clinically relevant interaction with amitriptyline, clonazepam, haloperidol or lorazepam is therefore unlikely. The *in vitro* experiments also suggested that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline, trazodone or fluoxetine. Bufuralol metabolism data from human liver microsomes suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

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 C_{max}, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy (see section 4.2 DOSE AND METHOD OF ADMINISTRATION - General Dosing Recommendations in Special Patient Populations (for dosing instructions for women taking hormonal contraceptives) and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE- Hormonal Contraceptives).

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 C_{max}, respectively. Measurement of serum FSH, LH and oestradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (see section 4.4 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 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 hepatic enzyme 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).

A study in healthy male volunteers found that there was a slightly enhanced elimination of lamotrigine in the presence of paracetamol but this was not considered to be clinically significant.

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} 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 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 a more potent inhibitor of OCT 2 than cimetidine, with IC50 values of 54 μM and 190 μM, respectively (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Fertility was reduced following oral administration of lamotrigine to male and female rats at a dose eliciting signs of toxicity (20 mg/kg/day). There is no experience of the effect of lamotrigine on human fertility.

Use in Pregnancy

Pregnancy Category: D

Lamotrigine should not be used in pregnancy unless, in the opinion of the doctor, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

Post-marketing data from several prospective pregnancy registries have documented outcomes in over 2000 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 case control study did not demonstrate an increased risk of oral clefts compared to other defects following exposure to lamotrigine.

The North American Antiepileptic Drug Pregnancy (NAAED) Registry has reported a marked and statistically significant increase in the rate of isolated oral cleft malformations. The observed prevalence of oral clefts was 24-fold higher than in the Brigham and Women's Hospital (BWH) birth malformation surveillance programme, the reference population for the registry. Overall, the NAAED registry identified five cases of oral clefts in 564 exposed women giving a prevalence rate of 8.9/1000.

In a pooled analysis of other pregnancy registries, the rate of isolated oral clefts with lamotrigine monotherapy was 4 in 2226 giving a prevalence rate of 1.79/1000. This prevalence is at the upper end of, but does not exceed, the rates for general population prevalence reported in the literature.

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

Lamotrigine is a weak inhibitor of dihydrofolate reductase and studies in rats have shown a decrease in folic acid during pregnancy. There is a theoretical risk of human fetal malformations when the mother is treated with a folate inhibitor during pregnancy.

It is recommended that women on antiepileptic drugs receive pre-pregnancy counselling with regard to the risk of fetal abnormalities. Women who are planning to become pregnant, or who are pregnant, while being treated with lamotrigine should take a folate supplement before conception and for the first 12 weeks of pregnancy, e.g. 5 mg folate daily. Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered to pregnant women.

Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the fetus. Anti-epileptic drugs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication. The risk to the mother and foetus of uncontrolled epilepsy should be considered when deciding on treatment options.

Reproductive toxicology studies with lamotrigine in mice, rats and rabbits at doses up to 100 mg/kg/day, 25 mg/kg/day and 30 mg/kg/day, respectively, did not reveal a clear teratogenic effect. An increased incidence of poorly ossified skeletal elements and rib anomalies, fetal weight decreases, prolonged gestation, fewer pups, increased incidence of still births and reduced pup viability during lactation, were observed in rats following administration of up to 25 mg/kg/day. These fetotoxic effects may have been due to maternal toxicity.

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 mothers. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

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

Lamotrigine and/or its metabolites pass into the milk of lactating rats (approximately 5% of the dose was transferred to the litter). Oral administration of lamotrigine 20 mg/kg/day to rats during late gestation and lactation was associated with reduced pup viability, concomitant with signs of maternal toxicity.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Two volunteer studies have demonstrated that the effect of lamotrigine on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with lamotrigine, adverse effects of a neurological nature such as dizziness and blurred vision have been reported. Therefore, patients should see how lamotrigine therapy affects them before driving or operating machinery.

In epilepsy: as there is individual variation in response to all antiepileptic drug therapy, patients should consult their physician on the specific issues of driving and epilepsy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects identified from epilepsy clinical trial data have been divided into indication specific sections. Additional adverse effects identified through post-marketing surveillance for both indications are included in the post-marketing section. All sections should be consulted when considering the overall safety profile of lamotrigine.

Epilepsy

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

In double blind, add-on, placebo controlled clinical trials in adults, skin rashes occurred in 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 in all clinical trials. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of lamotrigine.

Serious, potentially life-threatening skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell Syndrome) have been reported. Although the majority recover on drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4 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, which increases the mean half-life of lamotrigine nearly two-fold (see section 4.2 DOSE AND METHOD OF ADMINISTRATION)

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 below). 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.

The table below presents a comparison of adverse experiences reported during clinical trials with lamotrigine. Data are presented, in decreasing order of the incidence seen in patients taking lamotrigine, from the pooled placebo-controlled add-on studies that have been conducted with lamotrigine. For comparison, data are also presented from pooled monotherapy studies that have been conducted with lamotrigine. These adverse experiences have been reported most commonly during the initial weeks of treatment with lamotrigine.

TABLE OF ADVERSE EXPERIENCES FROM CLINICAL TRIALS					
Adverse Experience	**% Reporting from Pooled Add-on Studies[1]**		**% Reporting from Pooled Monotherapy Studies[2]**		
	Lamotrigine (n = 242)	**Placebo (n = 233)**	**Lamotrigine (n = 443)**	**Carbamazepine (n = 246)**	**Phenytoin (n = 95)**
Diplopia	21	8	< 1	3	2
Dizziness	19	12	8	14	12
Ataxia	19	5	< 1	6	12
Headache	17	14	20	17	19
Asthenia	16	18	16	24	29
Nausea	16	7	10	10	4
Somnolence	10	9	8	20	28
Vomiting	9	3	4	4	1
Respiratory Disorder	7	7	< 1	1	1
Rash	6	5	12	14	9
Pain	6	4	2	2	5
Pharyngitis	3	< 1	5	4	2
Flu syndrome	< 1	< 1	5	4	3
Insomnia	4	< 1	6	2	3
Menstrual disorder	1	< 1	1	5	Not reported
Tremor	3	2	2	< 1	8
Lung disorder	< 1	< 1	1	2	6
Depression	4	3	2	5	3
Amnesia	3	4	3	3	5
Thinking abnormality	2	2	2	4	5

[1] AEs with incidence ≥ 5% of patients taking lamotrigine tablets (includes corresponding rates for monotherapy events).
[2] AEs with incidence ≥ 5% in any treatment group (includes corresponding rates for add-on events).

Post-marketing Adverse Effects

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

The incidence of adverse reactions to marketed drugs, such as lamotrigine, is difficult to reliably assess due to the nature of spontaneous, voluntary reporting systems and the problems associated with estimating the total exposure to the drug. With these limitations in mind, the following data has been generated from post-marketing data collected for lamotrigine. The adverse experiences included are those believed to be probably causally related to lamotrigine (at least in some instances) and are grouped by body system with an estimate of the

frequency with which the reaction may be seen in the lamotrigine treated patient population (whether or not due to the drug in individual cases).

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).

FREQUENCY ESTIMATES OF ADVERSE REACTIONS SEEN WITH LAMOTRIGINE TABLETS FROM POST-MARKETING DATA

Gastrointestinal Disorders:

Very common: nausea, vomiting

Common: diarrhoea

Uncommon: anorexia

Blood and Lymphatic System Disorders:

Uncommon: transient leucopenia or thrombocytopenia

Very rare: lymphadenopathy

There have been reports of haematological abnormalities and lymphadenopathy that may or may not be associated with the hypersensitivity syndrome (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The haematological abnormalities have included neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia and very rarely, aplastic anaemia and agranulocytosis.

Immune System Disorders:

Very rare: hypersensitivity syndrome (DRESS) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Unknown: Haemophagocytic lymphohistiocytosis (HLH) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

There have been reports of HLH with use of lamotrigine. Most patients with HLH are acutely ill with multiorgan involvement. Common findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin and liver function and coagulation abnormalities.

Psychiatric Disorders:

Common: aggression, irritability

Uncommon: confusion

Very rare: tics, hallucinations, nightmares

Eye Disorders:

Very common: diplopia, blurred vision

Uncommon: conjunctivitis, photophobia

Nervous System Disorders:

Very common: headache, somnolence, ataxia, dizziness

Common: nystagmus, insomnia, tremor

Uncommon: agitation

Rare: aseptic meningitis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Very rare: increase in seizure frequency, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis

In children hyperkinesia has been reported (5%).

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.

Skin and Subcutaneous Tissue Disorders:

Very common: skin rash

Uncommon: erythema multiforme, Stevens-Johnson Syndrome, alopecia, photosensitivity reaction

Rare: exfoliative dermatitis, toxic epidermal necrolysis

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Musculoskeletal Disorders:

Very rare: rhabdomyolysis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), lupus-like reactions

General Disorders:

Common: tiredness

Hepatobiliary Disorders:

Elevations of liver functions tests and rare reports of hepatic dysfunction, including hepatic failure, have been reported. Hepatic dysfunction usually occurs in association with hypersensitivity reactions, but isolated cases have been reported without overt signs of hypersensitivity.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

Overdose has resulted in the following clinical features: nystagmus, ataxia, dizziness, somnolence, blurred vision, headache, vomiting, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has also been observed in overdose patients. Acute ingestion of doses in excess of 10 to 30 times the maximum therapeutic dose of lamotrigine, have been reported. Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal.

A patient who ingested a dose calculated to be between 4 and 5 g of lamotrigine was admitted to hospital with coma lasting 8 to 12 hours which was followed by recovery over the next two to three 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

No specific antidotes are available to treat overdosage. In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy as clinically indicated. Measures should be taken to protect the airway as consciousness may be impaired.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The precise mechanism of the anticonvulsant action of lamotrigine is not certain. The results of neurochemical and electrophysiological studies with various *in vitro* and *in vivo* preparations indicate that lamotrigine can inhibit voltage-gated sodium channels and reduce the release of glutamate, an excitatory amino acid implicated in the pathophysiology of epileptic seizures. It is possible that these effects underlie inhibition of the sustained repetitive firing of action potentials characteristic of neurons in epileptic foci, thereby limiting the spread of seizures.

In tests designed to evaluate the central nervous system effects of drugs, the results obtained using doses of lamotrigine 240 mg administered to healthy adult volunteers did not differ from placebo, whereas both phenytoin 1000 mg and diazepam 10 mg 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 carbamazepine 600 mg significantly impaired fine visual motor coordination 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 Trials

Adult Add-on Treatment of Partial and Generalised Seizures

The safety and efficacy of lamotrigine has been demonstrated in six double-blind, placebo-controlled, crossover studies (n = 221) with the duration of lamotrigine treatment ranging from 8 to 12 weeks, using doses up to 400 mg. Additionally, a double blind, placebo controlled, parallel study was performed of two fixed doses of lamotrigine (300 mg, n = 71; 500 mg, n = 72) versus placebo (n = 73). The median percentage reduction in total seizure count on lamotrigine, compared with placebo, significantly favoured lamotrigine in five of the six crossover trials. Overall 23% (range 7 to 67%) of patients in the controlled crossover trials showed a ≥ 50% reduction in total seizures in lamotrigine compared with placebo. In the controlled parallel study, the median reduction (%) from baseline in total seizures during weeks 13 to 24 was 14% on placebo compared with 23% on lamotrigine 300 mg and 32% on lamotrigine 500 mg.

The difference from placebo was statistically significant for lamotrigine 500 mg but not for lamotrigine 300 mg. The most common adverse experiences affected the central nervous system (ataxia, dizziness, diplopia) and occurred more frequently on lamotrigine 500 mg than lamotrigine 300 mg in the controlled parallel study. Across the controlled trials, approximately 10% of patients using lamotrigine developed a rash compared with 5% on placebo, with approximately 3% of patients on lamotrigine withdrawing with this adverse experience.

Adult Monotherapy

Two 48-week, double blind, randomised, active controlled (carbamazepine and phenytoin, respectively) clinical trials of lamotrigine monotherapy in the treatment of newly diagnosed epilepsy have been conducted. An additional randomised, active controlled (carbamazepine), open trial in this patient population has also been conducted. A total of 784 patients from these three studies were analysed (443 lamotrigine, 246 carbamazepine and 95 phenytoin). These studies indicate that the efficacy of lamotrigine monotherapy, in both generalised and partial seizures, may be comparable to that seen with carbamazepine and phenytoin. The escalation dose of lamotrigine in these studies that was associated with the lowest incidence of rash leading to withdrawal (2.2%) was 25 mg daily for the first two weeks, followed by 50 mg daily for the next two weeks, to achieve a maintenance

dose of 100 to 200 mg/day by weeks 5 to 6 (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Paediatric Add-on Therapy

The safety and efficacy of lamotrigine have been demonstrated in 285 children with refractory epilepsy aged 2 to 12 years in five open add-on trials of 48 weeks duration. Lamotrigine appeared effective in both partial and generalised seizure types. Across all seizure types, 34% of patients experienced ≥ 50% reduction in seizures. The modal maintenance dose was 5 to 15 mg/kg for those not taking valproate and 1 to 5 mg/kg for those taking valproate. 7% of patients discontinued lamotrigine with a rash. In patients on concomitant valproate, 2% withdrew with a rash when their daily dose of lamotrigine in the first week of treatment was ≤ 0.5 mg/kg compared with 13% withdrawn with rash at an initial dose of lamotrigine > 0.5 mg/kg. 155 patients aged 2 to 18 years (123 patients aged 12 years or under) continued to receive lamotrigine for up to four years. 4% of these patients withdrew because of adverse experiences. Lamotrigine had no effect on expected normal weight and height increases when taken for periods of up to four years.

Lennox-Gastaut Syndrome

Lamotrigine may be of benefit as add-on therapy for seizures associated with Lennox-Gastaut Syndrome.

One double blind, placebo controlled, add-on, parallel study has been performed in patients aged 3 to 25 years with Lennox-Gastaut syndrome. These patients were being treated with a combination of up to three anti-epileptic drugs including carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, lorazepam, nitrazepam, oxcarbazepine, phenobarbital (phenobarbitone), primidone, phenytoin, sodium valproate or vigabatrin. There are no data available on the use of lamotrigine as the sole drug treatment of Lennox-Gastaut Syndrome. No single drug is likely to be of benefit.

After a four-week run in period, patients (age range 2 to 28 years) were randomised to receive either lamotrigine (n = 79) (age range 3 to 25) or placebo (n = 90) for 16 weeks (including dose escalation period in the first six weeks of treatment) in addition to their existing therapy. Addition of lamotrigine to existing therapy resulted in a median reduction in counts of major motor seizures (drop attacks and tonic-clonic seizures) of 32% compared with a reduction of 9% in patients on existing therapy with add-on placebo. The results were also significantly in favour of lamotrigine when drop attacks and generalised tonic-clonic seizures were analysed separately, but not for atypical absence seizures. Rash was recorded in 7/79 lamotrigine add-on patients versus 4/90 placebo add-on patients. 4% of add-on lamotrigine patients and 8% of add-on placebo patients were withdrawn with adverse experiences. 3% discontinued lamotrigine because of rash compared with 1% on placebo. In the lamotrigine group, one patient was hospitalised because of rash and a second was reported to have developed Stevens-Johnson syndrome but did not require hospitalisation. 4% of patients on placebo and no patients on lamotrigine were withdrawn because of worsening seizures.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In healthy volunteers, lamotrigine is rapidly and completely absorbed from the gut. Peak plasma concentrations occur approximately 2.5 hours after oral drug administration.

Distribution

Lamotrigine 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

Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers, there is a modest induction of its own metabolism. Based on the available data, however, there is no clinical evidence that lamotrigine induces mono-oxygenase enzymes to an extent that would cause important interactions with drugs metabolised by these enzymes.

Ninety-four per cent of a radiolabelled dose of lamotrigine given to human volunteers was recovered in the urine over a period of 168 hours. Only 2% was recovered in the faeces. Lamotrigine is extensively metabolised in humans and the major metabolite is an N-glucuronide that accounts for 65% of the dose recovered in the urine. A further 8% of the dose is recovered in the urine as unchanged lamotrigine. High performance liquid chromatography radio detection revealed the presence of another N-glucuronide metabolite present at about one-tenth of the concentration of the major metabolite.

Excretion

The mean elimination half-life is 29 hours and the pharmacokinetic profile is linear up to 450 mg, the highest single dose tested. The half-life of lamotrigine is greatly affected by concomitant medication with a mean value of 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 sodium valproate alone (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Children (under 12 years)

Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults, with a mean value of approximately 7 hours when given with enzyme-inducing drugs, such as carbamazepine and phenytoin, and increasing to mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Elderly (65 to 76 years)

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

Renal Impairment

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were each given a single 100 mg 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' antiepileptic drugs (AEDs) regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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. Reduced doses should generally be used in patients with grade B or C hepatic impairment (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lamotrigine was not genotoxic in assays for gene mutation or chromosomal damage.

Carcinogenicity

There was no evidence of carcinogenicity following daily oral administration of lamotrigine to mice and rats for up to two years at doses of up to 30 and 10 mg/kg respectively.

Effect of lamotrigine on Cardiac Rhythm and Conduction

In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. Lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, it could slow ventricular conduction and increase the risk of arrhythmia in people with structural heart disease or myocardial ischemia. Elevated heart rates could also increase the risk of ventricular conduction slowing with lamotrigine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

LOGEM chewable/dispersible tablets contain the following inactive ingredients: cellulose - microcrystalline, sodium starch glycollate, povidone, silicon dioxide, saccharin sodium, blackcurrant flavouring 502009 AP0551 (PI Identifier: 1961), mannitol and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al blister pack

Pack sizes: 14, 28, 30, 56, 100

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 99059 - LOGEM 25 lamotrigine 25 mg chewable/dispersible tablet blister pack

AUST R 99062 - LOGEM 100 lamotrigine 100 mg chewable/dispersible tablet blister pack

AUST R 99064 - LOGEM 200 lamotrigine 200 mg chewable/dispersible tablet blister pack

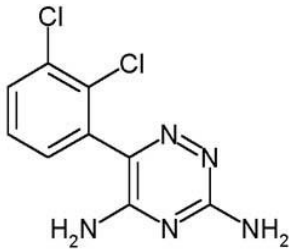
AUST R 99360 - LOGEM 50 lamotrigine 50 mg chewable/dispersible tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 3,5-diamino-6- (2,3-dichlorophenyl)- 1,2,4-triazine

Molecular formula: $C_9H_7N_5Cl_2$

Molecular weight: 256.09

Lamotrigine is a white to pale cream coloured powder.

Lamotrigine is a substituted asymmetric triazine. The pKa of lamotrigine at 25°C is 5.7. It is very slightly soluble in water and slightly soluble in ethanol and chloroform.

CAS Number

84057-84-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

17/03/2005

10 DATE OF REVISION

03/11/2023

Summary Table of Changes

Section Changed	Summary of New Information
4.4 & 5.3	At the request of the TGA, inclusion of specific heading and text for arrhythmia as a potential increased risk following findings from in vitro studies and a search of WHO adverse events database (Vigilyze).

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