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 DOSAGE AND ADMINISTRATION.)

NAME OF THE DRUG:

The chemical name for lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (CAS No.: 84057-84-1), and the chemical structure is:

![Chemical Structure of Lamotrigine]

Lamictal Dispersible/Chewable Tablets contain lamotrigine.

DESCRIPTION:

Lamotrigine is a substituted asymmetric triazine. It is a white to pale cream-coloured powder. It is slightly soluble in ethanol and chloroform, and very slightly soluble in water. The pKa of lamotrigine at 25°C is 5.7. Each Lamictal Dispersible/Chewable tablet also contains calcium carbonate, hydroxypropyl cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone, saccharin sodium, magnesium stearate and blackcurrant flavour.

PHARMACOLOGY:

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 epilepsy. It is possible that these effects underlie inhibition of the sustained repetitive firing of action potentials characteristic of neurones 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 240 mg lamotrigine administered to healthy adult 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 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.
PHARMACOKINETICS

Absorption
In healthy volunteers, lamotrigine is rapidly and completely absorbed from the gut. The peak plasma concentration occurs 2.5 hours after oral drug administration.

Distribution
Lamotrigine is 55% bound to plasma proteins; it is 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 percent 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 man and the major metabolite is an N-glucuronide which 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 radiodetection revealed the presence of another N-glucuronide metabolite present at about one-tenth of the concentration of the major metabolite.

Elimination
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 enzyme inducing drugs such as carbamazepine and phenytoin, and increasing to a mean of approximately 70 hours when co-administered with sodium valproate alone (see DOSAGE AND ADMINISTRATION).

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 5 years. The half-life of lamotrigine is generally shorter in children than in adults with a mean 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 DOSAGE AND 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 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 (0.39mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450mg.
Renal Impairment

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing hemodialysis 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 hemodialysis), and 1.57 mL/min/kg (during hemodialysis) 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 hemodialysis) and 13.0 hours (during hemodialysis), 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 hemodialysis 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 PRECAUTIONS).

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 DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Adult Add-on Treatment of Partial and Generalised Seizures

The efficacy and safety of lamotrigine has been demonstrated in 6 double blind, placebo controlled, crossover studies (n=221) with duration of lamotrigine treatment ranging from 8 - 12 weeks, using doses up to 400 mg. Additionally, a double blind, placebo controlled, parallel study was performed of 2 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 5 of the 6 crossover trials. Overall 23% (range 7 - 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 - 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 commonest adverse experiences affected the central nervous system (ataxia, dizziness, diplopia) and occurred more frequently on 500 mg lamotrigine than 300 mg lamotrigine in the controlled parallel study. Across the controlled trials, approximately 10% of patients on 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 - 6 (see DRUG INTERACTIONS AND ADVERSE EVENTS).
Paediatric Add-on Therapy
The safety and efficacy of lamotrigine has been demonstrated in 285 children with refractory epilepsy aged 2 to 12 years in 5 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 - 15 mg/kg for those not taking valproate and 1 - 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 4 years. 4% of these patients withdrew because of adverse experiences. Lamotrigine had no effect on expected normal weight and height increase when taken for periods of up to 4 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 3 antiepileptic drugs including carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, lorazepam, nitrazepam, oxcarbazepine, phenobarbitalone, 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 4 week run in period, patients (age range 2 - 28 years) were randomised to receive either lamotrigine (n=79) (age range 3 - 25) or placebo (n=90) for 16 weeks (including dose escalation period in the first 6 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.

INDICATIONS
Lamictal is an antiepileptic drug for the treatment of partial and generalised seizures in adults and children.

There is extensive experience with Lamictal used initially as “add-on” therapy. The use of Lamictal has also been found to be effective as monotherapy following withdrawal of concomitant antiepileptic drugs.

Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended. (See CLINICAL TRIALS.)
CONTRAINDICATIONS

Lamotrigine is contraindicated in individuals with known hypersensitivity to lamotrigine, or to any other ingredient in Lamictal Tablets (see COMPOSITION).

PRECAUTIONS

Skin Rash

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

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 rashes such as Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). (See ADVERSE REACTIONS). 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 DOSAGE AND ADMINISTRATION).

- Concomitant use of valproate, which increases the mean half life of lamotrigine nearly two fold (see DOSAGE AND ADMINISTRATION).

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

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. **It is important to note that early manifestations of hypersensitivity (eg. 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.**

As with other antiepileptic drugs 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 antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or other antiepileptic drugs are added-on to lamotrigine monotherapy, considerations should be given to the effect this may have on lamotrigine pharmacokinetics (see DRUG INTERACTIONS).

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy:

An ethinyloestradiol/levonorgestrel (30 mcg / 150 mcg) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see Interactions). Following titration, higher maintenance doses of lamotrigine (by as much as two fold) may be needed 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 "General Dosing Recommendations for Lamotrigine in Special Patient Populations, Dosage and Administration".

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

Other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine on hormonal contraceptive efficacy:

An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinyloestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (see 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, ie, breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine is a weak inhibitor of dihydrofolate reductase, hence there is a possibility of interference with folate metabolism during long-term therapy. During prolonged human dosing, however, 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.

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.
Hepatic Impairment

Lamotrigine is cleared primarily by metabolism in the liver. Lamotrigine should be administered with caution in patients with hepatic impairment as clearance is reduced. Refer to DOSAGE AND ADMINISTRATION: Hepatic Impairment.

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

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.

Carcinogenicity, Mutagenicity, Impairment of Fertility

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

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.

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

Use in Pregnancy (CategoryD)

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 2000 women exposed to lamotrigine monotherapy during the first trimester of pregnancy. 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 foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

It is recommended that women on antiepileptic drugs receive prepregnancy counselling with regard to the risk of foetal 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, for example 5 mg of 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 foetus. Antiepileptic 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, foetal 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 25mg/kg/day. These foetotoxic effects may have been due to maternal toxicity.

Use During Lactation
There is limited information on the use of Lamotrigine in lactation. Preliminary data indicate that lamotrigine passes into breast milk in concentrations usually of the order of 40-60% of the plasma concentration. In a small number of infants known to have been breastfed, the plasma concentrations of lamotrigine reached levels at which pharmacological effects may occur. The potential benefits of breast-feeding should be weighed against the potential risk of adverse effects occurring in the infant.

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.

Driving
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 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.

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.

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

Increases in the plasma concentrations of other antiepileptic drugs have been reported in a few patients, however controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant antiepileptic drugs. Evidence from in vitro studies indicates that lamotrigine does not displace other antiepileptic drugs from protein binding sites.

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.
Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, 30 mcg ethinyloestradiol/150 mcg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and 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.

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 ethinyloestradiol 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 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 PRECAUTIONS). 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 AEDs

Antiepileptic drugs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce hepatic drug-metabolising enzymes enhance the metabolism of lamotrigine (see DOSAGE AND ADMINISTRATION). Other drug-classes which induce hepatic drug-metabolising enzymes may also enhance the metabolism of lamotrigine.

Sodium valproate, which competes with lamotrigine for hepatic drug metabolising enzymes, reduces the metabolism of lamotrigine and increases the mean half life of lamotrigine nearly two fold (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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.

Interactions involving other psychoactive agents

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

In a steady-state pharmacokinetic interaction study in healthy adult volunteers, daily doses of 15 mg olanzapine reduced the AUC and Cmax of lamotrigine by an average of 24% and 20%, respectively. An effect of this magnitude is not generally expected to be clinically relevant. Lamotrigine at 200 mg daily dose did not affect the pharmacokinetics of olanzapine.
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.

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 DOSAGE AND 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.

ADVERSE REACTIONS

In double-blind, add-on placebo controlled, clinical trials, 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 PRECAUTIONS).

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 DOSAGE AND ADMINISTRATION)

- Concomitant use of valproate, which increases the mean half life of lamotrigine nearly two fold (see DOSAGE AND 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 multiorgan failure. It is important to note that early manifestations of hypersensitivity (eg. 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 lamotrigine patients, 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.

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<tr>
<th>Adverse Experience</th>
<th>% Reporting from Pooled Add-on Studies&lt;sup&gt;1&lt;/sup&gt;</th>
<th>% Reporting from Pooled Monotherapy Studies&lt;sup&gt;2&lt;/sup&gt;</th>
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<td>Menstrual disorder</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lung disorder</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Amnesia</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Thinking abnormality</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

- Not reported

Irritability/aggression, tiredness, drowsiness, agitation, confusion and hallucinations have also been reported. In children hyperkinesia has been reported (5%). Very rarely, lupus-like reactions have been reported.

Arthralgia was reported commonly during the clinical development program for lamotrigine in bipolar disorder.

There have been reports of haematological abnormalities which may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leucopenia,
anaemia, thrombocytopenia, pancytopenia, and very rarely aplastic anaemia and agranulocytosis.

Movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor have also been reported. 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.

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.

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 table below 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).

<table>
<thead>
<tr>
<th>FREQUENCY ESTIMATES OF ADVERSE REACTIONS SEEN WITH LAMOTRIGINE FROM POST-MARKETING DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Digestive Disorders</td>
</tr>
<tr>
<td>Haematological Disorders</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
</tr>
<tr>
<td>Dermatological Disorders</td>
</tr>
<tr>
<td>Common: Rash</td>
</tr>
<tr>
<td>Uncommon: Erythema multiforme, Stevens Johnson Syndrome</td>
</tr>
<tr>
<td>Rare: Exfoliative dermatitis, toxic epidermal necrolysis</td>
</tr>
</tbody>
</table>

Frequency estimates: Common: more than one per hundred patients. Uncommon: between one per thousand and one per hundred patients. Rare: fewer than one per thousand patients. Very Rare: fewer than one per ten thousand patients.

DOSAGE AND 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 Precautions). 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
Pharmacokinetics), 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 lamotrigine 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 (eg 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).

When concomitant antiepileptic drugs are withdrawn to achieve lamotrigine monotherapy or
other antiepileptic drugs (AEDs) are added-on to treatment regimens containing lamotrigine,
consideration should be given to the effect this may have on lamotrigine pharmacokinetics
(see DRUG INTERACTIONS).

**Add-on Therapy in Adults and Children over 12 years of age:**
The initial lamotrigine 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 1-2 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 those patients taking sodium valproate, the initial lamotrigine dose is 25 mg every alternate
day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should
be increased by a maximum of 25-50 mg every 1-2 weeks until the optimal response is
achieved. The usual maintenance dose is 100 to 200 mg/day given once a day or 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 patients taking anti-epileptic drugs where the pharmacokinetic interaction with lamotrigine is
currently not known (see DRUG INTERACTIONS), the dose escalation as recommended for
lamotrigine with concurrent valproate, should be used presently.
### TABLE 1
**ADD-ON THERAPY IN ADULTS AND CHILDREN OVER 12 YEARS**
*(Total daily dose in mg/day)*

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1 &amp; 2</th>
<th>Weeks 3 &amp; 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sodium valproate*</td>
<td>50 (once a day)</td>
<td>100 (divided doses)</td>
<td>200 - 400 (divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 100 mg every 1-2 weeks</td>
</tr>
<tr>
<td>With sodium valproate</td>
<td>12.5 (given as 25 mg on alternate days)</td>
<td>25 (once a day)</td>
<td>100 - 200 (once a day or divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>To achieve maintenance, doses may be increased by 25-50 mg every 1-2 weeks</td>
</tr>
</tbody>
</table>

*Escalation Dose from Clinical Trials in Monotherapy

25 (once a day) | 50 (once a day) | 100 - 200 (once a day or divided doses)

*E.g. phenytoin, carbamazepine, phenobarbitone and primidone.*

**NOTE:** In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used presently.

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see **PRECAUTIONS**).

**Add-on Therapy in Children aged 2 to 12 years:**
In those patients taking enzyme inducing AEDs with/without other AEDs (except valproate) the initial lamotrigine dose is 0.6 mg/kg bodyweight/day given 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 1-2 weeks until optimal response is achieved.

The usual maintenance dose is 5-15 mg/kg bodyweight/day given as a divided dose, with a maximum of 400 mg/day (see **TABLE 2**).

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 patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see **DRUG INTERACTIONS**), the dose escalation as recommended for lamotrigine with concurrent valproate, should be used.
### TABLE 2
ADD-ON THERAPY IN CHILDREN AGED 2 TO 12 YEARS
(Total daily dose in mg/kg bodyweight/day)

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1 &amp; 2</th>
<th>Weeks 3 &amp; 4</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sodium valproate*</td>
<td>0.6 (divided doses)</td>
<td>1.2 (divided doses)</td>
<td>1.2 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 5 - 15 mg/kg (two divided doses) to a maximum of 400 mg/day.</td>
</tr>
<tr>
<td>With sodium valproate</td>
<td>0.15** (once a day)</td>
<td>0.3 (once a day)</td>
<td>0.3 mg/kg increments every 1-2 weeks to achieve a maintenance dose of 1 - 5 mg/kg (once a day or divided doses) to a maximum of 200 mg/day.</td>
</tr>
</tbody>
</table>

*e.g. phenytoin, carbamazepine, phenobarbitone and primidone.

NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for lamotrigine with concurrent valproate, should be used presently.

** NOTE: If the calculated dose is 1-2 mg then 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.

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

Add-on Therapy in Children under 2 years
To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. If the doses calculated for children, according to bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

Due to the very limited safety, efficacy, pharmacokinetic and dosing data that are available in children under 2 years old, dosing in this age group should only be initiated within a specialist unit. There are no data available on the use of lamotrigine in neonates. In particular the use of lamotrigine in patient less than 2 years old, who are also taking sodium valproate, is not recommended. This is due to the difficulties in providing an accurate initial dose.

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see PRECAUTIONS).

General Dosing Considerations for Add-on Therapy:
For patients receiving lamotrigine in combination with other antiepileptic drugs, whether or not optimal dosing has been achieved, a re-evaluation of all antiepileptic 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 PRECAUTIONS).

Withdrawal of Concomitant Antiepileptic Drugs
The dose of lamotrigine following the withdrawal of concomitant antiepileptic 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 antiepileptic 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 antiepileptic drugs (eg sodium valproate) (see PRECAUTIONS and DRUG INTERACTIONS).

Discontinuation of lamotrigine in patients with epilepsy:

As with other antiepileptic 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

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 PRECAUTIONS & 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 an enzyme inhibitor of lamotrigine e.g. valproate; whether lamotrigine is added to an enzyme inducer of lamotrigine e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampin; or whether lamotrigine is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin.

(b) Starting hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking enzyme inducers of lamotrigine:
The maintenance dose of lamotrigine may need to be increased by as much as two-fold according to the individual clinical response (see PRECAUTIONS & INTERACTIONS).

(c) Stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and NOT taking enzyme inducers of lamotrigine:
The maintenance dose of lamotrigine may need to be decreased by as much as 50% according to the individual clinical response (see PRECAUTIONS & INTERACTIONS).

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 more 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, lamotrigine 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 Lamictal 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).
OVERDOSAGE

Symptoms and signs
Overdose has resulted in the following clinical features: nystagmus, ataxia, dizziness, somnolence, blurred vision, headache, vomiting, impaired consciousness, increased seizures and coma. Acute ingestion of doses in excess of 10 to 30 times the maximum therapeutic dose has 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 lamotrigine was admitted to hospital with coma lasting 8 - 12 hours, followed by recovery over the next 2 - 3 days. A further patient who ingested 5.6 g lamotrigine was found unconscious. Following treatment with activated charcoal for suspected intoxication the patient recovered after sleeping for 16 hours.

Treatment
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. Measures should be taken to protect the airway as consciousness may be impaired.

PRESENTATION

Lamictal Dispersible/Chewable tablets 2 mg are white to off-white round tablets, with an odour of blackcurrant. They are marked "LTG 2" on one side and engraved with two overlapping super-ellipses on the other.

Lamictal Dispersible/Chewable tablets 5 mg are white to off-white, elongated, biconvex tablets, unscored, with an odour of blackcurrant. They are marked "GS CL2" on one side and "5" on the other.

Lamictal Dispersible/Chewable tablets 25 mg, 50 mg, 100 mg and 200 mg are white to off-white, multifaceted super elliptical tablets with an odour of blackcurrant. The 25 mg tablet is marked "Lamictal 25" on one side and unscored on the other side, the 50 mg tablet is marked "Lamictal 50" on one side and unscored on the other side, the 100 mg tablet is marked "Lamictal 100" on one side and unscored on the other side; and the 200 mg tablet is marked "Lamictal 200" on one side and unscored on the other side.

All presentations of Lamictal tablets are available in packs of 56 tablets with the exception of the 2 mg tablets which are also available in packs of 30 tablets.

STORAGE

All Lamictal tablets should be stored below 30°C. All of the tablets should also be kept in a position where they will remain dry and Lamictal Dispersible/Chewable tablets 25 mg, 50 mg, 100 mg and 200 mg should be protected from light.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155
Approval by the Therapeutic Goods Administration: 7 March 2006
Date of Safety Related Notification: 5 April 2006

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