PRODUCT MONOGRAPH

NU-LAMOTRIGINE

Lamotrigine Tablets

25, 100 and 150 mg Tablets

ANTIEPILEPTIC

NU-PHARM INC.
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PRODUCT MONOGRAPH

NU-LAMOTRIGINE

Lamotrigine Tablets

25, 100 and 150 mg

THERAPEUTIC CLASSIFICATION

Antiepileptic

This product does not have dosage strengths small enough to initiate treatment in children under 12 years of age.

Do not exceed the recommended initial dose and subsequent dose escalations of NU-LAMOTRIGINE (lamotrigine). More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS).

ACTIONS AND CLINICAL PHARMACOLOGY

Lamotrigine is a drug of the phenyltriazine class chemically unrelated to existing antiepileptic drugs (AEDs).

Lamotrigine is thought to act at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit the release of excitatory amino acid neurotransmitters (*i.e.* glutamate and aspartate) that are thought to play a role in the generation and spread of epileptic seizures.

CLINICAL TRIALS

In adult placebo-controlled clinical studies, lamotrigine has been shown to be effective in reducing seizure frequency and the number of days with seizures when added to existing antiepileptic drug

therapy in adult patients with partial seizures, with or without generalized tonic-clonic seizures, that are not satisfactorily controlled.

The effectiveness of lamotrigine adjunctive therapy has also been shown in pediatric and adult patients with Lennox-Gastaut syndrome. A significant reduction in major motor seizures, drop attacks, and tonic-clonic seizures were seen following lamotrigine treatment compared with placebo treated patients. Improvements in cognitive skills (speech, nonverbal communication, alertness, attention and intellectual capacity), behaviour and fine co-ordination have been seen with lamotrigine treatment in these patients.

Studies have also been conducted using lamotrigine monotherapy in adult patients (n = 443) newly diagnosed with epilepsy (partial seizures, with or without secondary generalization or primary generalized tonic clonic). Results have shown comparable efficacy (time to first seizure, seizure frequency and percentage of patients seizure-free) with fewer side effects than currently approved therapies.

Clinical trials have also demonstrated that adult patients (any seizure type) can be converted to lamotrigine monotherapy from polytherapy with significant numbers of patients maintaining or improving seizure control. Efficacy was maintained during long-term treatment (up to 152 weeks).

A 24-week monotherapy trial was conducted in elderly newly diagnosed patients (102 patients received lamotrigine and 48 received carbamazepine). The findings indicate comparable efficacy, and demonstrate that lamotrigine was well tolerated in the elderly. However, the small and unbalanced number of patients in the study precludes any firm conclusions on the relative safety of the two drugs.

PHARMACOKINETICS

Adults

Lamotrigine is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours (T_{max}) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single lamotrigine doses of 50 to 400 mg, peak plasma concentration (C_{max} = 0.6 to 4.6 mcg/mL) and the area under the plasma concentration-versus-time curve (AUC = 29.9 to 211 h.mcg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ($t_{1/2}$) and volume of distribution (Vd/F) are independent of dose. The $t_{1/2}$ averages 33 hours after single doses and Vd/F ranges from 0.9 to 1.4 L/kg. Following repeated dosing in healthy volunteers for 14 days, the $t_{1/2}$ decreased by an average of 26% (mean steady state $t_{1/2}$ of 26.4 hours) and plasma clearance increased by an average of 33%. In a single-dose study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%.

Lamotrigine is approximately 55% bound to human plasma proteins. This binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital or valproic acid. Lamotrigine does not displace other antiepileptic drugs (carbamazepine, phenytoin and phenobarbital) from protein binding sites.

Lamotrigine is metabolized predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-N-glucuronide conjugate that can be hydrolyzed by β-glucuronidase. Approximately 70% of an oral lamotrigine dose is recovered in urine as this metabolite.

Pediatrics

Lamotrigine was rapidly absorbed in children, with a T_{max} ranging from 1 to 6 hours. The mean Vd/F of lamotrigine in children aged 5 to 11 years (1.3 to 1.4 L/kg) was similar to those seen in adults (0.9 to 1.4 L/kg) but was larger in younger children (1.8 to 2.3 L/kg). As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. While the CL/F was higher and $t_{1/2}$ was shorter in younger children than in older children, the mean CL/F was higher and mean $t_{1/2}$ was shorter in both pediatric groups than in adults. Population analysis results showed that the estimated apparent plasma clearances in patients aged 13 to 18 years were similar to those found in adult patients.

Elderly (≥65 years)

Results of a population pharmacokinetic analysis, based on individual trials in which both adult (n=138) and elderly (n=13) patients with epilepsy were enrolled, indicated that the clearance of lamotrigine in elderly patients did not change to a clinically relevant extent. After single doses, apparent clearance was lower in the elderly by 12% (31 mL/min at age 70 vs. 35 mL/min at age 20). After 48 weeks of treatment, the difference in clearance was 10% (37 mL/min at age 70 vs. 41 mL/min at age 20). In addition, the pharmacokinetics of lamotrigine were studied in 12 healthy elderly volunteers who each received a single oral dose of 150 mg. The mean clearance in the elderly (0.39 mL/min) lies within the range of mean clearance values (0.31 to 0.65 mL/min) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg (see also DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS).

Renal Impairment

The pharmacokinetics of a single oral dose of lamotrigine (100 mg) were evaluated in 12 individuals with chronic renal failure (with mean creatinine clearance of 13 mL/min) who were not receiving other antiepileptic drugs. In this study, the elimination half-life of unchanged lamotrigine was prolonged (by an average of 63%) relative to individuals with normal renal function (see PRECAUTIONS – Renal Failure and DOSAGE AND ADMINISTRATION).

Hemodialysis

In six hemodialysis patients, the elimination half-life of unchanged lamotrigine was doubled off dialysis, and reduced by 50% on dialysis, relative to individuals with normal renal function.

Hepatic Impairment

A single dose pharmacokinetic study was performed in 24 subjects with hepatic impairment (n=12 mild/Grade A; n=5 moderate/Grade B and n=7 severe/Grade C), vs. 12 healthy controls. For the moderate and severe subgroups, the mean values for AUC and plasma half-life were increased approximately twofold and threefold respectively over control values, with clearance decreased proportionately. For the mild group, while mean values were not statistically different from those of controls, a subgroup of 1-4 subjects (dependant on pharmacokinetic parameter examined) showed abnormal individual values which were in the range of the moderately impaired subjects (see also DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Gilbert's Syndrome

Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) does not appear to affect the pharmacokinetic profile of lamotrigine.

Concomitant Antiepileptic Drugs

In patients with epilepsy, concomitant administration of lamotrigine with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine $t_{1/2}$ to 13 hours. Concomitant administration of lamotrigine with valproic acid significantly increases $t_{1/2}$ and decreases the clearance of lamotrigine, whereas concomitant administration of lamotrigine with valproic acid plus enzyme-inducing AEDs can prolong $t_{1/2}$ up to approximately 27 hours. Chronic administration of acetaminophen was shown to slightly decrease the $t_{1/2}$ and increase the clearance of a single dose of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1, and for pediatric patients in Table 2:

Table 1. Mean pharmacokinetic parameters in adult patients with epilepsy or healthy volunteers

Lamotrigine Administered		Healthy Young Volunteers		Patients With Epilepsy		
		Lamotrigine	Lamotrigine + Valproic Acid**	Lamotrigine + EIAEDs	Lamotrigine + Valproic Acid	Lamotrigine + Valproic Acid + EIAEDs
T_{max} (hr)	Single Dose	2.2 (0.25-12.0)*	1.8 (1.0-4.0)	2.3 (0.5-5.0)	4.8 (1.8-8.4)	3.8 (1.0-10.0)
	Multiple Dose	1.7 (0.5-4.0)	1.9 (0.5-3.5)	2.0 (0.75-5.93)	ND	ND
$T_{1/2}$ (hr)	Single Dose	32.8 (14.0-103.0)	48.3 (31.5-88.6)	14.4 (6.4-30.4)	58.8 (30.5-88.8)	27.2 (11.2-51.6)
	Multiple Dose	25.4 (11.6-61.6)	70.3 (41.9-113.5)	12.6 (7.5-23.1)	ND	ND
Plasma Clearance (mL/min/kg)	Single Dose	0.44 (0.12-1.10)	0.30 (0.14-0.42)	1.10 (0.51-2.22)	0.28 (0.16-0.40)	0.53 (0.27-1.04)
	Multiple Dose	0.58 (0.24-1.15)	0.18 (0.12-0.33)	1.21 (0.66-1.82)	ND	ND

EIAEDs =Enzyme-Inducing Antiepileptic Drugs. ND = Not done.
* Range of individual values across studies.
** Valproic acid administered chronically (multiple dose study) or for 2 days (single dose study).

Table 2. Mean pharmacokinetic parameters in pediatric patients with epilepsy				
Pediatric Study Population	**Number of Subjects**	**T_{max} (hr)**	**$t_{1/2}$ (hr)**	**CL/F (mL/min/kg)**
Ages 10 Months To 5.3 Years				
Patients Taking EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients Taking AEDs With No Known Effect On Drug Metabolizing Enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients Taking VPA Only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5 To 11 Years				
Patients Taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients Taking EIAEDs And VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients Taking VPA Only*	3	4.5 (3.0-6.0)	55.4 (24.3-73.7)	0.31 (0.20-0.54)
Ages 13 To 18 Years				
Patients Taking EIAEDs	11	†	†	1.3
Patients Taking EIAEDs And VPA	8	†	†	0.5
Patients Taking VPA Only	4	†	†	0.3

VPA = Valproic acid. EIAEDs = Enzyme-Inducing Antiepileptic Drugs. ND = Not done.

* Two subjects were included in the calculation for mean T_{max}

† Parameter not estimated

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of lamotrigine was measured and compared following oral administration of a single 1 x 150 mg dose of NU-LAMOTRIGINE (lamotrigine) or Lamictal® (lamotrigine) tablets, under fasting and fed conditions. The results from measured data are summarized in Tables 3 - A and B below, respectively:

Table 3-A: Summary Table of the Comparative Bioavailability Data Under Fasting Conditions
Lamotrigine (Dose: 1 x 150 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu-lamotrigine	Lamictal®†	
AUC_{0-72} (ng•hr/mL)	64344 65595 (21)	62630 64032 (22)	102.7
AUC_I (ng•hr/mL)	82702 90561 (61)	83533 100484 (94)	99.0
C_{max} (ng/mL)	1961 1972 (11)	2037 2071 (18)	96.3
T_{max} (hr)*	2.07 (47)	1.52 (55)	-
$t_{1/2}$ (hr)*	34.2 (67)	40.1 (107)	-

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Lamictal® is manufactured by Glaxo Wellcome Inc., and was purchased in Canada.

Table 3-B: Summary Table of the Comparative Bioavailability Data Under Fed Conditions
Lamotrigine (Dose: 1 x 150 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu-lamotrigine	Lamictal®†	
AUC_T (ng•hr/mL)	57240 58343 (21)	55105 56073 (20)	103.9
AUC_I (ng•hr/mL)	73939 78732 (43)	71396 76631 (45)	103.5
C_{max} (ng/mL)	1671 1679 (10)	1638 1642 (8)	102.1
T_{max} (hr)*	3.41 (26)	3.56 (19)	-
$t_{1/2}$ (hr)*	32.9 (39)	33.5 (47)	-

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Lamictal® is manufactured by Glaxo Wellcome Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

NU-LAMOTRIGINE (lamotrigine) is indicated:

– as adjunctive therapy for the management of adult patients with epilepsy who are not satisfactorily controlled by conventional therapy,

– for use as monotherapy in adults following withdrawal of concomitant antiepileptic drugs, and

– as adjunctive therapy for the management of the seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients.

CONTRAINDICATIONS

NU-LAMOTRIGINE (lamotrigine) is contraindicated in patients with known hypersensitivity to lamotrigine or to any components of the formulation.

WARNINGS

This product does not have dosage strengths small enough to initiate treatment in children under 12 years of age.

SERIOUS RASHES ASSOCIATED WITH HOSPITALIZATION HAVE OCCURRED WITH THE USE OF LAMOTRIGINE. THE INCIDENCE OF THESE RASHES IN CLINICAL TRIALS WAS 1% (1/100) IN PEDIATRIC PATIENTS (AGE < 16 YEARS) AND 0.3% (3/1000) IN ADULTS. THE INCIDENCE OF SERIOUS RASH REPORTED AS STEVENS-JOHNSON SYNDROME (SJS) IN CLINICAL TRIALS WAS 0.5% (1/200) IN PEDIATRIC PATIENTS AND 0.1% (1/1000) IN ADULTS. IN WORLDWIDE POST-MARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR DEATH ASSOCIATED WITH RASH HAVE BEEN

REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

A HIGHER INCIDENCE OF SERIOUS DERMATOLOGIC EVENTS (see PRECAUTIONS - Skin-Related Events, Tables 4 and 5; see also DOSAGE AND ADMINISTRATION) HAS BEEN ASSOCIATED WITH MORE RAPID INITIAL TITRATION (EXCEEDING THE RECOMMENDED INITIAL DOSE OR EXCEEDING THE RECOMMENDED DOSE ESCALATION), AND USE OF CONCOMITANT VALPROIC ACID.

NEARLY ALL CASES OF RASH ASSOCIATED WITH LAMOTRIGINE HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK SIGNALED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMOTRIGINE, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE LIFE THREATENING. ACCORDINGLY, ALL PATIENTS WHO DEVELOP RASH SHOULD BE PROMPTLY EVALUATED AND LAMOTRIGINE WITHDRAWN IMMEDIATELY, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.

Hypersensitivity Reactions

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 ADVERSE REACTIONS). 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.

Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (*e.g.* fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

PRECAUTIONS

Drug Discontinuation

Abrupt discontinuation of any antiepileptic drug (AED) in a responsive patient with epilepsy may provoke rebound seizures. In general, withdrawal of an AED should be gradual to minimize this risk. Unless safety concerns (*i.e.* rash) require a more rapid withdrawal, the dose of lamotrigine should be tapered over a period of at least two weeks (see DOSAGE AND ADMINISTRATION).

Occupational Hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials common adverse effects included dizziness, ataxia, drowsiness, diplopia and blurred vision. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that lamotrigine does not affect them adversely.

Skin-Related Events

In adult controlled studies of adjunctive lamotrigine therapy, the incidence of rash (usually maculopapular and/or erythematous) in patients receiving lamotrigine was 10% compared with 5% in placebo patients. The rash usually occurred within the first six weeks of therapy and resolved during continued administration of lamotrigine. Lamotrigine was discontinued because of rash in 1.1% of adult patients in controlled studies and 3.8% of all patients in all studies. The rate of rash-related withdrawal in clinical studies was higher with more rapid initial titration dosing, and in patients receiving concomitant valproic acid (VPA), particularly in the absence of enzyme-inducing AEDs (see Tables 4 and 5; see also WARNINGS and DOSAGE AND ADMINISTRATION).

Table 4. Effect of concomitant AEDs on rash associated with lamotrigine in all adult controlled and uncontrolled clinical trials regardless of dosing escalation scheme.

AED Group	Total Patient Number	All Rashes	Withdrawal Due To Rash	Hospitalization In Association With Rash
EIAEDs*	1788	9.2%	1.8%	0.1%
EIAEDs* + VPA	318	8.8%	3.5%	0.9%
NEIAEDs ± VPA**	159	20.8%	11.9%	2.5%
NEIAEDs**	27	18.5%	0.0%	0.0%

VPA = Valproic acid.
* EIAEDs = Enzyme-Inducing Antiepileptic Drugs, include carbamazepine, phenobarbital, phenytoin and primidone.
** NEIAEDs = Non-Enzyme-Inducing Antiepileptic Drugs, include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin and gabapentin.

Table 5. Effect of the initial daily dose* of lamotrigine in the presence of concomitant AEDs, on the incidence of rash leading to withdrawal of treatment in adult add-on clinical trials.

AED Group	EIAEDs**		EIAEDs** + VPA		NEIAEDs*** ± VPA	
LAM Average Daily Dose	Total Patient Number	% of Patients Withdrawn	Total Patient Number	% of Patients Withdrawn	Total Patient Number	% of Patients Withdrawn
12.5 mg	9	0.0	10	0.0	51	7.8
25 mg	3	0.0	7	0.0	58	12.1
50 mg	182	1.1	111	0.9	35	5.7
100 mg	993	1.4	179	4.5	15	40.0
125 mg	601	2.8	11	18.2	0	0.0

LAM = Lamotrigine. VPA = Valproic acid.

* Average daily dose in 1 week.

** EIAEDs = Enzyme-Inducing Antiepileptic Drugs, include carbamazepine, phenobarbital, phenytoin and primidone.

*** NEIAEDs = Non-Enzyme-Inducing Antiepileptic Drugs, include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin and gabapentin.

Increased incidence of rash-related withdrawal was seen when initial doses were higher and titration more rapid than recommended under DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Antiepileptic Drugs (AEDs)

Lamotrigine does not affect the plasma concentrations of concomitantly administered enzyme-inducing AEDs. Antiepileptic drugs that induce hepatic drug-metabolizing enzymes (phenytoin, carbamazepine, phenobarbital and primidone) increase the plasma clearance and reduce the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY).

Valproic acid reduces the plasma clearance and prolongs the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY). When lamotrigine was administered to 18 healthy volunteers already receiving valproic acid, a modest decrease (25% on average) in the trough steady-state valproic acid plasma concentrations was observed over a 3-week period,

followed by stabilization. However, the addition of lamotrigine did not affect the plasma concentration of valproic acid in patients receiving enzyme-inducing AEDs in combination with valproic acid (see PRECAUTIONS - Skin-Related Events).

The net effects of co-administration of lamotrigine with phenytoin, carbamazepine or valproic acid are summarized in Table 6 below:

Table 6. Summary of AED interactions with lamotrigine

AED	AED Plasma Concentration With Adjunctive LAM*	LAM Plasma Concentration With Adjunctive AEDs**
Phenytoin (PHT)	No significant effect	↓ 50%
Carbamazepine (CBZ)	No significant effect	↓ 40%
CBZ Epoxide***	Conflicting data	
Valproic Acid (VPA)	Decreased	↑ 200%
VPA + PHT And/Or CBZ	Not evaluated	No significant effect

LAM = Lamotrigine. AED = Antiepileptic Drugs.
* From adjunctive clinical trials and volunteer studies.
** Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.
*** Not administered, but an active metabolite of carbamazepine.

Oral Contraceptives

In a study of 12 female volunteers, lamotrigine did not affect plasma concentrations of ethinyloestradiol and levonorgestrel following administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, the patient should be asked to report any change in the menstrual bleeding pattern.

Drugs Depressing Cardiac Conduction

See Patients With Special Diseases And Conditions - Cardiac Conduction Abnormalities.

Drug/Laboratory Test Interactions

Lamotrigine has not been associated with any assay interferences in clinical laboratory tests.

USE IN PEDIATRICS

This product does not have dosage strengths small enough to initiate treatment in children under 12 years of age (see WARNINGS).

Safety and efficacy in patients below the age of 16 years, other than those with Lennox-Gastaut Syndrome, have not been established.

Use in the Elderly

As the pharmacokinetics in this age group do not differ significantly from a non-elderly adult population, no dosage adjustment from the recommended adult schedule is required (see also DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Use in Obstetrics

Pregnancy: Studies in mice, rats and rabbits given lamotrigine orally or intravenously revealed no evidence of teratogenicity; however, maternal and secondary fetal toxicity were observed. Studies in rats and rabbits indicate that lamotrigine crosses the placenta; placental and fetal levels of lamotrigine were low and comparable to levels in maternal plasma. Because animal reproduction studies are not always predictive of human response, lamotrigine should only be used during pregnancy if the benefits of therapy outweigh the risks associated with it.

Clinical trial data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, its effects during human fetal development are unknown.

To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, before fetal outcome (*e.g.* ultrasound, results of amniocentesis, birth, etc.) is known, in the Lamotrigine Pregnancy Registry by calling 1-800-336-2176 (toll free).

Labour and Delivery: The effect of lamotrigine on labor and delivery in humans is unknown.

Nursing Mothers: There is limited information on the use of lamotrigine in lactation. Preliminary data indicate that lamotrigine passes into human milk in concentrations usually of the order 40-60% of the serum concentration. In a small number of infants known to have been breast fed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur. Because of the potential for adverse reactions from lamotrigine in nursing infants, breast-feeding while taking this medication is not recommended.

Patients With Special Diseases and Conditions

Clinical experience with lamotrigine in patients with concomitant illness is limited. Caution is advised when using lamotrigine in patients with diseases or conditions that could affect the metabolism or elimination of the drug.

Renal Failure: A study in individuals with chronic renal failure (not receiving other AEDs) indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY). Use of lamotrigine in patients with severe renal impairment should proceed with caution.

Hepatic Impairment: This product does not have dosage strengths small enough to initiate treatment in patients with impaired hepatic function.

Cardiac Conduction Abnormalities: One placebo-controlled trial that compared electrocardiograms at baseline and during treatment demonstrated a mild prolongation of the P-R interval associated with lamotrigine administration. The prolongation was statistically significant but clinically insignificant. Patients with significant cardiovascular disease or electrocardiographic abnormalities were, however, systematically excluded from clinical trials. Thus, lamotrigine should be used with caution in patients with cardiac conduction abnormalities, and in patients taking concomitant medications which depress AV conduction.

Dependence Liability

No evidence of abuse potential has been associated with lamotrigine, nor is there evidence of psychological or physical dependence in humans.

Laboratory Tests

The use of lamotrigine does not require routine monitoring of any clinical laboratory parameters or plasma levels of concomitant AEDs.

ADVERSE REACTIONS

RARELY, SERIOUS SKIN RASHES, INCLUDING STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS (LYELL SYNDROME) HAVE BEEN REPORTED. ALTHOUGH THE MAJORITY RECOVER FOLLOWING DRUG WITHDRAWAL, SOME

PATIENTS EXPERIENCE IRREVERSIBLE SCARRING AND THERE HAVE BEEN RARE CASES OF ASSOCIATED DEATH (see WARNINGS).

Adverse experiences in patients receiving lamotrigine were generally mild, occurred within the first two weeks of therapy, and resolved without discontinuation of the drug.

Commonly Observed

The most commonly observed adverse experiences associated with the use of adjunctive therapy with lamotrigine (incidence of at least 10%) were dizziness, headache, diplopia, somnolence, ataxia, nausea and asthenia.

Dizziness, diplopia, ataxia and blurred vision were dose-related and occurred more commonly in patients receiving carbamazepine in combination with lamotrigine than in patients receiving other enzyme-inducing AEDs with lamotrigine. Reduction of the daily dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or lamotrigine may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic acid, or non-inducing AEDs (see WARNINGS and PRECAUTIONS - Skin-Related Events**,** Table 4).

Adverse Events Associated With Discontinuation of Treatment

Across all adult add-on studies, the most common adverse experiences associated with discontinuation of lamotrigine were rash, dizziness, headache, ataxia, nausea, diplopia, somnolence, seizure exacerbation, asthenia and blurred vision. In controlled clinical trials, 6.9% of the 711 patients receiving lamotrigine discontinued therapy due to an adverse experience,

versus 2.9% of the 419 patients receiving placebo. Of 3501 patients and volunteers who received lamotrigine in pre-marketing clinical studies, 358 (10.2%) discontinued therapy due to an adverse experience.

Serious Adverse Events Associated With Discontinuation of Treatment

Discontinuation due to an adverse experience classified as serious occurred in 2.3% of adult patients and volunteers who received lamotrigine in the pre-marketing studies. Rash accounted for almost half of the discontinuations due to serious adverse experiences. More rapid initial titration of lamotrigine, and concomitant use of valproic acid were associated with higher incidences of rash-related withdrawal in clinical studies (see WARNINGS and PRECAUTIONS - Skin-Related Events**,** Table 5).

Adult Controlled Add-On Clinical Studies

Table 7 enumerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with lamotrigine.

Other Events Observed During Clinical Studies: During clinical testing, multiple doses of lamotrigine were administered to 3501 patients and volunteers. The conditions and duration of exposure to lamotrigine during these clinical studies varied greatly. Studies included monotherapy and pediatric trials. A substantial proportion of the exposure was gained in open, uncontrolled clinical studies. Adverse experiences associated with exposure to lamotrigine were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse

events without first grouping similar types of adverse experiences into a smaller number of standardized event categories.

Since the adverse experiences reported occurred during treatment with lamotrigine in combination with other AEDs, they were not necessarily caused by lamotrigine.

The following adverse events have been reported on one or more occasions by at least 1% of patients and volunteers exposed to lamotrigine: anorexia, weight gain, amnesia, concentration disturbance, confusion, emotional lability, nervousness, nystagmus, paresthesia, thinking abnormality and vertigo (all types of events are included except those already listed in Table 7).

Adult Monotherapy Clinical Studies

Withdrawals due to adverse events were reported in 42 (9.5%) of newly diagnosed patients treated with lamotrigine monotherapy. The most common adverse experiences associated with discontinuation of lamotrigine were rash (6.1%), asthenia (1.1%), headache (1.1%), nausea (0.7%) and vomiting (0.7%).

Elderly Monotherapy Clinical Studies

A study with elderly newly-diagnosed patients yielded rates of adverse events which were generally similar to those reported in adults (see Table 7). The rate of withdrawal due to adverse events was 21.6%, with rash (3%), nausea (3%) and coordination abnormalities (3%) representing the most common events associated with withdrawal, followed by somnolence (2%), depression (2%), accidental injury (2%) and malaise (2%) (see also DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Adjunctive Therapy in Lennox-Gastaut Syndrome

In 169 adult and pediatric patients with Lennox-Gastaut syndrome, 3.8% of patients on lamotrigine and 7.8% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with lamotrigine and deterioration of seizure control for patients treated with placebo. Fever and infection occurred at least 10% more frequently in patients ≤12 years of age than in patients >12 years of age on lamotrigine. Rash occurred at least 10% more frequently in female patients than male patients on lamotrigine. Table 8 lists adverse events that occurred in at least 1% of 79 adult and pediatric patients who received lamotrigine up to 15 mg/kg per day or a maximum of 400 mg/kg per day.

Table 7 – Percentage of Treatment-Emergent Adverse Experiences in Adult Placebo or Comparator-Controlled Clinical Studies[1]

	Adults (Adjunctive Therapy)		Elderly (Monotherapy)
Total number of Patients	**Lamotrigine (and other AEDs) (n=711)**	**Placebo (and other AEDs) (n=419)**	**Lamotrigine (n=102)**
Body System/Adverse Experience[2]			
Body as a Whole			
Headache	29.1	19.1	8.8
Accidental Injury	9.1	8.6	8.8
Asthenia	8.6	8.8	4.9
Flu Syndrome	7.0	5.5	4.9
Pain	6.2	2.9	5.9
Back Pain	5.8	6.2	3.9
Fever	5.5	3.6	0.9
Abdominal Pain	5.2	3.6	3.9
Infection	4.4	4.1	5.9
Neck Pain	2.4	1.2	0
Malaise	2.3	1.9	4.9
Seizure Exacerbation	2.3	0.5	n/a
Cardiovascular			
Chest pain	n/a	n/a	2.9
Syncope	n/a	n/a	2.9
Cerebrovascular accident	n/a	n/a	3.9
Digestive			
Nausea	18.6	9.5	8.8
Vomiting	9.4	4.3	8.8
Diarrhea	6.3	4.1	6.9
Dyspepsia	5.3	2.1	5.9
Constipation	4.1	3.1	8.9

Table 7 – Percentage of Treatment-Emergent Adverse Experiences in Adult Placebo or Comparator-Controlled Clinical Studies[1]

	Adults (Adjunctive Therapy)		Elderly (Monotherapy)
Total number of Patients	**Lamotrigine (and other AEDs) (n=711)**	**Placebo (and other AEDs) (n=419)**	**Lamotrigine (n=102)**
Body System/Adverse Experience[2]			
Tooth Disorder	3.2	1.7	0
Musculoskeletal			
Myalgia	2.8	3.1	0.9
Arthralgia	2.0	0.2	2.9
Nervous			
Dizziness	38.4	13.4	9.8
Ataxia	21.7	5.5	0
Somnolence	14.2	6.9	11.8
Incoordination	6.0	2.1	12.7
Insomnia	5.6	1.9	3.9
Tremor	4.4	1.4	0.9
Depression	4.2	2.6	4.9
Anxiety	3.8	2.6	0.9
Convulsion	3.2	1.2	1.9
Irritability	3.0	1.9	0
Speech Disorder	2.5	0.2	0.9
Memory Decreased	2.4	1.9	n/a
Memory Decreased (memory rating question)	n/a	n/a	19.6
Respiratory			
Rhinitis	13.6	9.3	0.9
Pharyngitis	9.8	8.8	1.9
Cough increased	7.5	5.7	2.9
Respiratory disorder	5.3	5.5	0.9
Asthma			3.0
Skin and Appendages			
Rash	10.0	5.0	8.8
Pruritus	3.1	1.7	5.9
Herpes Zoster	n/a	n/a	3.0
Eczema	n/a	n/a	2.0
Ulcer skin	n/a	n/a	2.0
Special Senses			
Diplopia	27.6	6.7	0
Blurred vision	15.5	4.5	0
Vision abnormality	3.4	1.0	0
Urogenital			
Female Patients	**(n=365)**	**(n=207)**	**(n=47)**
Dysmenorrhea	6.6	6.3	n/a
Menstrual disorder	5.2	5.8	n/a
Vaginitis	4.1	0.5	0

1. Patients from the studies summarized in the first two columns were receiving 1 to 3 concomitant enzyme-inducing antiepileptic drugs in addition to lamotrigine or placebo. Patients from the single study summarized in the last column were compared to n=48 patients receiving carbamazepine. Patients may have reported multiple adverse experiences during the study or at discontinuation. Thus, patients may be included in more than one category.
2. All adverse experiences reported by at least 2% of patients treated with either lamotrigine add-on or monotherapy are included.

Table 8. Treatment-emergent Adverse Experience Incidence in Placebo-controlled Add-on Trial in Adult and Pediatric Patients with Lennox-Gastaut Syndrome*

Body System/ Adverse Experience	Percent Of Patients Receiving Lamotrigine (n = 79)	Percent Of Patients Receiving Placebo (n = 90)
Body As A Whole		
Infection	13	8
Accidental Injury	9	7
Flu Syndrome	5	0
Asthenia	3	1
Abdominal Pain	3	0
Back Pain	1	0
Edema Of The Face	1	0
Lab Test Abnormal	1	0
Pain	1	0
Cardiovascular		
Hemorrhage	3	0
Digestive		
Vomiting	9	7
Constipation	5	2
Diarrhea	4	2
Nausea	4	1
Anorexia	3	1
Stomatitis Aphtha	1	0
Tooth Disorder	1	0
Endocrine		
Cushing's Syndrome	1	0
Hypothyroidism	1	0
Hemic And Lymphatic		
Lymphadenopathy (Enlarged Cervical Nodes)	1	0
Nervous System		
Ataxia	4	1
Convulsions	4	1
Tremor	3	0
Agitation	1	0
Coordination	1	0
Dizziness	1	0
Emotional Lability	1	0
Nervousness	1	0
Vertigo	1	0
Respiratory		
Pharyngitis	14	10
Bronchitis	9	7
Pneumonia	3	0
Dyspnea	1	0

Table 8. Treatment-emergent Adverse Experience Incidence in Placebo-controlled Add-on Trial in Adult and Pediatric Patients with Lennox-Gastaut Syndrome*

Body System/ Adverse Experience	Percent Of Patients Receiving Lamotrigine (n = 79)	Percent Of Patients Receiving Placebo (n = 90)
Skin		
Rash	9	7
Eczema	4	0
Nail disorder	1	0
Special Senses		
Blepharitis	1	0
Conjunctivitis	1	0
Keratitis	1	0
Ear Pain	1	0
Eye Pain	1	0
Urogenital		
Urinary Tract Infection	3	0
Balanitis	2	0
Penis Disorder	2	0

* The most frequently reported adverse reactions in children ≤12 years of age in both treatment groups were pharyngitis, fever and infection.

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of lamotrigine, the following adverse experiences have been reported in patients receiving marketed lamotrigine and from worldwide non-controlled investigative use. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation.

Blood and Lymphatic: There have been reports of hematological abnormalities which may or may not be associated with hypersensitivity syndrome. These have included disseminated intravascular coagulation, hemolytic anemia, neutropenia, leucopenia, pancytopenia, anemia, thrombocytopenia, red cell aplasia, and very rarely agranulocytosis and aplastic anemia.

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis. Elevations of liver function 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.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Neurology: Hallucinations. Exacerbation of parkinsonian symptoms in patients with pre-existing Parkinson's disease and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition. Movement disorders such as tics and unsteadiness have also been reported.

Non-site Specific: Hypersensitivity reaction, multiorgan failure, progressive immunosupression.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Adults

Acute ingestion of doses in excess of 20 times the maximum therapeutic dose has been reported. In general, overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.

However, there has been one fatality reported, a 22 year old female who intentionally ingested 15 g of lamotrigine. The patient experienced acute clonic seizures and heart failure, then became asystolic and was resuscitated, but she died 2 days later.

Pediatrics

Among patients ≤16 years of age, the two highest known single doses of lamotrigine have been 3 g by a 14 year old female and approximately 1 g by a 4 year old male. The 14 year old female was taking marketed lamotrigine; after the dose, she lost consciousness and was admitted to the hospital for supportive therapy, where she recovered fully (time to recovery not reported). The 4 year old male was drowsy and agitated when found, and his condition worsened to coma level II after hospitalization. He was given supportive therapy, and his condition improved rapidly with full recovery in 3 days.

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the body was removed during 4 hours of hemodialysis.

DOSAGE AND ADMINISTRATION

General

NU-LAMOTRIGINE (lamotrigine) is intended for oral administration and may be taken with or without food. NU-LAMOTRIGINE should be added to the patient's current antiepileptic therapy.

Valproic acid more than doubles the elimination half-life of lamotrigine and reduces the plasma clearance by 50%; conversely, hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital and primidone reduce the elimination half-life of lamotrigine by 50% and double the plasma clearance (see ACTION AND CLINICAL PHARMACOLOGY). These clinically important interactions require dosage schedules of NU-LAMOTRIGINE as summarized in Tables 9 to 12.

NU-LAMOTRIGINE does not alter plasma concentrations of concomitantly administered enzyme-inducing AEDs, and therefore, they do not usually require dose adjustment to maintain therapeutic plasma concentrations. For patients receiving NU-LAMOTRIGINE in combination with other AEDs, an evaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed. If there is a need to discontinue therapy with NU-LAMOTRIGINE, a step-wise reduction of dose over at least two weeks (approximately 50% per week) is recommended unless safety concerns (*i.e.* rash) require a more rapid withdrawal (see WARNINGS and PRECAUTIONS).

The relationship of plasma concentration to clinical response has not been established for lamotrigine. Dosing of NU-LAMOTRIGINE should be based on therapeutic response. In controlled clinical studies, doses of lamotrigine that were efficacious generally produced steady-state trough plasma lamotrigine concentrations of 1 to 4 µg/mL in patients receiving one or more concomitant AEDs. Doses of lamotrigine producing this plasma concentration range were well tolerated. As with any AED, the oral dose of NU-LAMOTRIGINE should be adjusted to the needs of the individual patient, taking into consideration the concomitant AED therapy the patient is receiving.

Adults and Children Over 12 Years of Age

Do not exceed the recommended initial dose and subsequent dose escalations of NU-LAMOTRIGINE. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS). For patients taking AEDs whose pharmacokinetic interactions with lamotrigine are currently unknown, follow the titration schedule for concomitant valproic acid and non-enzyme-inducing AEDs.

Table 9. NU-LAMOTRIGINE added to valproic acid with enzyme-inducing AEDs[1] in patients over 12 years of age

		*For Information Only**
		Patients Taking VPA *only* or VPA and NEIAEDs[2]
Weeks 1 + 2	25 mg once a day	*25 mg every other day*
Weeks 3 + 4	25 mg twice a day	*25 mg once a day*
Usual Maintenance	To achieve maintenance, doses may be increased by 25 to 50 mg every 1 to 2 weeks Usual dose is between 50 to 100 mg twice a day	To achieve maintenance, doses may be increased by 25 to 50 mg every 1 to 2 weeks Usual dose is between 50 to 100 mg twice a day

VPA = Valproic acid. AED = Antiepileptic Drugs.
1. EIAEDs = Enzyme-Inducing Antiepileptic Drugs, include carbamazepine, phenobarbital, phenytoin and primidone.
2. NEIAEDs = Non-Enzyme-Inducing Antiepileptic Drugs
* *Column reflects dosage recommendations in the United Kingdom and is provided for information.*

Table 10. NU-LAMOTRIGINE added to enzyme-inducing AEDs[1] (without valproic acid) in patients over 12 years of age.	
Weeks 1 + 2	50 mg once a day
Weeks 3 + 4	50 mg twice a day
Usual Maintenance	To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks Usual dose is between150 to 250 mg twice a day
VPA = Valproic acid. AED = Antiepileptic Drugs. 1. EIAEDs = Enzyme-Inducing Antiepileptic Drugs, include carbamazepine, phenobarbital, phenytoin and primidone.	

There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on lamotrigine therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the

addition of lamotrigine under these conditions is associated with a higher incidence of serious rash or rash-related withdrawal, even at an initial titration dose of 12.5 mg daily (see PRECAUTIONS - Skin-Related Events, Tables 4 and 5; see also WARNINGS). The potential medical benefits of the addition of NU-LAMOTRIGINE under these conditions must be weighed against the increased risk of serious rash. If use of NU-LAMOTRIGINE under these conditions is considered clinically indicated, titration should proceed with extreme caution, especially during the first six weeks of treatment.

Withdrawal of Concomitant AEDS in Adults

Concomitant AEDs may be decreased over a 5-week period, by approximately 20% of the original dose every week. However, a slower taper may be used if clinically indicated. During this period, the dose of NU-LAMOTRIGINE administered will be dependent upon the effect of the drug being withdrawn on the pharmacokinetics of lamotrigine, together with the overall clinical response of the patient. The withdrawal of enzyme inducing AEDs (*i.e.* phenytoin, phenobarbital, primidone and carbamazepine) will result in an approximate doubling of the $t_{1/2}$ of lamotrigine. Under these conditions, it may be necessary to reduce the dose of NU-LAMOTRIGINE. In contrast, the withdrawal of enzyme inhibiting AEDs (*i.e.* valproic acid) will result in a decrease in the $t_{1/2}$ of lamotrigine and may require an increase in the dose of NU-LAMOTRIGINE.

Pediatric Dosing

This product does not have dosage strengths small enough to initiate treatment in children under 12 years of age.

Elderly Patients (≥65 years of age)

No dosage adjustment from the recommended adult schedule is required. The pharmacokinetics of lamotrigine in this age group do not differ significantly from a non-elderly population (see also ACTION AND CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

Patients With Impaired Renal Function

The elimination half-life of lamotrigine is prolonged in patients with impaired renal function (see ACTION AND CLINICAL PHARMACOLOGY). Caution should be exercised in dose selection for patients with impaired renal function.

Patients With Impaired Hepatic Function

This product does not have dosage strengths small enough to initiate treatment in patients with impaired hepatic function.

PHARMACEUTICAL INFORMATION

Drug Substance

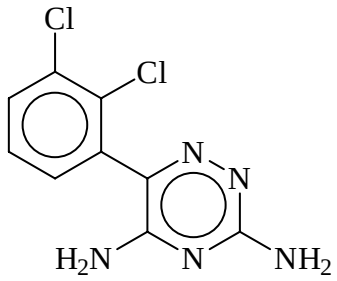
Trade Name: NU-LAMOTRIGINE

Common Name: Lamotrigine

Chemical Names: 1) 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine

2) 3,5-Diamino-6-(2,3-dichlorophenyl)-*as*-triazine

Structural Formula:



Molecular Formula: $C_9H_7Cl_2N_5$

Molecular Weight: 256.09

Description: Lamotrigine is a white to off-white powder that is non-hydroscopic and has moderate surface area and porosity. It has a melting point between 215 to 219°C, the pH of a saturated water solution is 6.88, and the pKa is 5.7. It is soluble in dimethylformamide, slightly soluble in acetone, and very slightly soluble in water (0.153 g/L).

Composition

In addition to the active ingredient lamotrigine, each NU-LAMOTRIGINE tablet contains the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, yellow aluminum lake (100 mg tablets only) and yellow ferric oxide (150 mg tablets only).

Stability and Storage Recommendations

Store at room temperature (15 to 30°C) in tight containers.

AVAILABILITY OF DOSAGE FORMS

NU-LAMOTRIGINE 25 mg Tablets: Each white, shield-shaped, flat faced, bevelled edge tablet, scored and engraved "25" on one side, contains 25 mg of lamotrigine. Available in bottles of 100 and 500 tablets

NU-LAMOTRIGINE 100 mg Tablets: Each peach, shield-shaped, flat faced, bevelled edge tablet, scored and engraved “LAM” over "100" on one side, contains 100 mg of lamotrigine. Available in bottles of 100 and 500 tablets

NU-LAMOTRIGINE 150 mg Tablets: Each cream, shield-shaped, flat faced, bevelled edge tablet, scored and engraved “LAM” over "150" on one side, contains 150 mg of lamotrigine. Available in bottles of 60 and 100 tablets.

INFORMATION TO THE PATIENT

The information provided below is for patients, or parents of patients, who will be receiving NU-LAMOTRIGINE (lamotrigine). Please read the following information carefully before you start to take NU-LAMOTRIGINE, even if you have taken this drug before. Please do not discard this leaflet; you may need to read it again.

WHAT IS NU-LAMOTRIGINE

NU-LAMOTRIGINE, the trade name for lamotrigine, has been prescribed to you/your child to control your/their epilepsy. Please follow your doctor's recommendations carefully.

BEFORE TAKING NU-LAMOTRIGINE

Please inform your doctor if you/your child:

– ever had an unusual or allergic reaction to NU-LAMOTRIGINE,

– are/is allergic to any component of NU-LAMOTRIGINE tablets,

– are/is pregnant or are planning to become pregnant,

– are/is breast-feeding (nursing),

– are/is taking any other prescription or over-the-counter medicine,

– have/has liver or kidney disease, or other medical conditions, or

– consume alcohol on a regular basis.

HOW TO TAKE NU-LAMOTRIGINE

– It is very important that you/your child take NU-LAMOTRIGINE exactly as your doctor instructed.

– This product does not have dosage strengths small enough to initiate treatment in children under 12 years of age or in patients with liver problems.

– Your doctor may increase or decrease your/your child's medication according to your/their specific needs. Carefully follow the instructions you were given. Do not change the dose yourself.

– Do not stop taking your medication abruptly, because your/your child's seizures may increase.

– If you/your child happens to miss a dose, do not try to make up for it by doubling up on the dose next time. Just take/give the next regularly scheduled dose and try not to miss any more.

– NU-LAMOTRIGINE may be taken with or without food.

– Consult your doctor before taking/giving your child any other medication, including over-the-counter medicines. Some drugs can produce various side-effects when they are used in combination with NU-LAMOTRIGINE.

– It is important to keep your/your child's appointments for medical checkups.

PRECAUTIONS WHILE TAKING NU-LAMOTRIGINE

– If you/your child develops **fever, rash, swollen lymph nodes, hives, sore mouth, sore eyes or swelling of lips or tongue**, particularly in the first six weeks of therapy, contact your doctor immediately.

– Your doctor will monitor your/your child's response to NU-LAMOTRIGINE on a regular basis. However, if **your/your child's seizures get worse***,* tell your doctor immediately.

– Different side-effects have been reported by patients taking lamotrigine. These effects were generally mild and **included dizziness, headaches, double vision (diplopia), poor coordination (ataxia), nausea, blurred vision, sleepiness/drowsiness (somnolence), nasal congestion (rhinitis) and rash.** However, this does not mean that you/your child will experience such effects, because people can react in different ways to the same medicine.

– If you/your child experiences **dizziness, blurred vision, poor coordination, headaches, drowsiness, or similar effects, it is very important that you/your child does not perform any hazardous tasks such as driving or operating machinery.** Consult your doctor.

– If you/your child notices any bothersome or unusual effects while taking NU-LAMOTRIGINE check with your doctor or pharmacist right away.

– Do not stop taking/giving NU-LAMOTRIGINE unless directed by your doctor. Always check that you have an adequate supply of NU-LAMOTRIGINE. Remember that this medicine was prescribed only for you/your child, never give it to anyone else.

WHAT TO DO IN CASE OF AN OVERDOSE

If you/your child accidentally takes an overdose of NU-LAMOTRIGINE, contact your doctor or the nearest hospital emergency, even though you/your child may not feel sick.

HOW TO STORE NU-LAMOTRIGINE

Store your NU-LAMOTRIGINE tablets at room temperature (15 to 30^{o}C), in tight containers. Cap the bottle tightly immediately after use. **Keep out of reach of children.**

WHAT DO NU-LAMOTRIGINE TABLETS CONTAIN

Each NU-LAMOTRIGINE tablet contains the active ingredient lamotrigine.

If you have any other questions please ask your pharmacist or doctor.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

In Vivo Studies

In *in vivo* studies in animal models, lamotrigine has an antiepileptic profile suggesting utility in the treatment of partial seizures and generalized tonic-clonic seizures. Lamotrigine was effective in the maximal electroshock (MES), maximum pentylenetetrazol, electrically evoked after discharge (EEAD) tests and in visually evoked after discharge (VEAD) tests. In mice and rats, lamotrigine has a longer duration of action than phenytoin, carbamazepine, diazepam or valproate. Lamotrigine's potency is similar to that of phenytoin (mouse), phenobarbital (rat), carbamazepine (rat) and diazepam (mouse) (see Table 11).

Table 11. Potency and duration of lamotrigine following maximal electroshock-induced seizures.

	ED_{50} For Abolition Of Hind Leg Extension (mg/kg/p.o.)		**Duration Maintenance Of Peak Activity (hours)**	
Drug	**Mouse**	**Rat**	**Mouse**	**Rat**
Lamotrigine	2.6 to 3.8	1.9 to 3.3	1 to 8	1 to 8
Phenytoin	3.5	19.7	8	1
Phenobarbital	9.1	4.7	1	1
Carbamazepine	6.9	2.5	1	0.25
Valproate	332.4	238	0.25	1
Diazepam	3.2	16.9	1	1

In single-dose mouse and rat studies, the anticonvulsant ED_{50}s of orally administered lamotrigine ranged from 1.9 to 3.8 mg/kg. Signs of CNS toxicity did not occur until high multiples of the lamotrigine ED_{50}s were reached, and consisted of ataxia and tremors (at 140 mg/kg), and convulsions (at 300 and 675 mg/kg in mice and rats, respectively). In multiple-dose studies in mice and rats, the anticonvulsant ED_{50}s were unchanged. In mice, lamotrigine was well tolerated at chronic doses up to 30 mg/kg/day. In rats, convulsions possibly related to drug administration

were rarely observed (in no more than 1 of 46 to 49 animals per dose group) and did not occur until week 24 of chronic oral dosing with 15 mg/kg/day.

Preclinical Pharmacokinetics

Lamotrigine was found to accumulate in the kidney of the male rat, bind to melanin-containing ocular tissue of the pigmented rat and cynomolgus monkey, and prolong gastric emptying time in rats. In dogs, lamotrigine was extensively metabolized to a 2-N-methyl metabolite which produced dose-dependent prolongations of the P-R interval and QRS duration in ECG tracings in this species. Only trace amounts of this metabolite (< 0.6% of lamotrigine dose) were found in human urine. Clinical studies showed no evidence in humans for manifestations of these preclinical observations regarding accumulation in the kidney, melanin binding, gastric emptying or cardiac effects.

In Vitro Studies

In vitro pharmacological studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit the release of excitatory amino acid neurotransmitters (*i.e.* glutamate and aspartate) that are thought to play a role in the generation and spread of epileptic seizures.

Lamotrigine was shown to be a weak inhibitor of dihydrofolate reductase *in vitro.* In clinical studies, lamotrigine did not affect blood folate concentrations or associated hematologic parameters.

TOXICOLOGY

Acute Toxicity

Single-dose lethality values were calculated in male and female mice and rats receiving lamotrigine by the oral and intravenous routes of administration. The calculated LD_{50} values are listed in Table 12.

Table 12. Acute toxicity studies.

Route	LD_{50} Dose (mg/kg)			
	Mouse		Rat	
	Female	Male	Female	Male
Oral	245	292	205	163
I.V.	141	134	107	112

The lowest doses (mg/kg) at which any deaths occurred were 300 (oral) and 125 (I.V.) in mice and 140 (oral) and 100 (I.V.) in rats. Deaths were seen as early as 1 minute following I.V. dosing and 30 minutes following oral dosing. The most severe sign noted was clonic convulsions (rats only). Other signs, including tremors, ataxia, hypoactivity, decreased respiration and hypothermia were also observed. Survivors generally recovered within 24 hours, but hypoactivity lasted for several days in some animals.

Long-Term Toxicity

Subacute to subchronic (14 to 30 days) studies were conducted in rats (oral and intravenous), marmosets (oral) and cynomolgus monkeys (intravenous).

Effects seen in rats which were considered to be consistently associated with oral lamotrigine administration included specific nephropathy (males, 1 mg/kg/day), increased weight of stomach

contents (6.25 mg/kg/day), increased water consumption and urine output (10 mg/kg/day), reduced weight gain and food consumption (22.5 mg/kg/day), and convulsions (50 mg/kg/day).

Marmosets were given either single daily lamotrigine doses of 10 to 100 mg/kg/day or 3 daily doses ranging from 10 to 50 mg/kg/dose. The following effects were observed at the following lowest doses given: slight decreases in WBC, RBC and related values at 100 mg/kg/day or 22.5 mg/kg/dose t.i.d., post-dose incoordination, slight body weight loss, decreased food consumption (50 mg/kg/day or 22.5 mg/kg/dose t.i.d.); post-dose salivation and vomiting (10 mg/kg/day or 22.5 mg/kg/dose t.i.d.). Blood, brain and liver folate levels were not affected.

In a 14-day intravenous study in cynomolgus monkeys, daily lamotrigine doses ranged from 5 to 20 mg/kg. The following effects were observed (shortly after dosing) at the following lowest doses given: ataxia, vomiting and decreased food consumption (10 mg/kg); nystagmus (15 mg/kg); agitation, slight body weight loss (20 mg/kg).

In chronic oral toxicity studies, mice were given daily lamotrigine doses of up to 60 mg/kg for 90 days. Rats were given doses of up to 30 mg/kg/day for 90 days, up to 25 mg/kg/day for 6 months, and up to 15 mg/kg/day for one year. The only effect seen in mice was increased stomach content weight, likely related to delayed gastric emptying (30 and 60 mg/kg/day). The most prominent drug-related effects in rats were renal histopathological changes, seen at all dose levels, other effects seen were similar to those documented in the subacute and subchronic rat studies. Other species were also evaluated by light microscopic examination of kidney sections from animals given lamotrigine and by in *vitro* studies of kidney cortex slice uptake of radio-labelled lamotrigine. The studies demonstrated that the renal effects seen are limited to male rats and represent exacerbation of spontaneous hyaline droplet changes related to the renal proximal tubular handling of α_{2u}-globulin. This globulin is a specific protein synthesized by the

liver in male rats only. The hyaline droplets are secondary lysosomes and contain α_{2u}-globulin. Lamotrigine is also accumulated in the renal proximal tubular epithelium in the form of rectilinear and crystalline inclusions which likely contain both α_{2u}-globulin and lamotrigine. Time-and-dose dependent loading of these cells leads to cellular degeneration and eventual regeneration. Changes are consistent with those seen in "light hydrocarbon nephropathy", a male-rat-specific condition, which is reversible following termination of treatment and has no human counterpart.

Cynomolgus monkeys were treated with daily oral lamotrigine doses of up to 20 mg/kg in 13, 26 and 52-week studies. Effects noted were limited to animals given 20 mg/kg/day and included post-dose ataxia, lethargy, trembling, locomotor incoordination and convulsions in some animals in the 26-week study. A reduced rate of body weight gain and transient weight loss was seen at doses as low as 5 mg/kg/day, but only in the 52-week study.

Carcinogenicity

There was no evidence of carcinogenicity in mice treated orally with lamotrigine (10 to 30 mg/kg/day) for up to 106 weeks. Lamotrigine was not carcinogenic in two rat studies where animals received doses of 1 to 10 mg/kg/day for up to 104 weeks (females) or 112 weeks (males). In both studies, survival was not affected by treatment.

Mutagenicity

In vitro, lamotrigine was not mutagenic in microbial (Ames) or mammalian (mouse lymphoma) mutagenicity tests with or without metabolic activation. Lamotrigine had no effect on the incidence of chromosomal abnormalities in cultured human lymphocytes exposed to

concentrations of up to 1000 mcg/mL in the presence or absence of S9 metabolic activation. Concentrations of 500 and 1000 mcg/mL without activation were cytotoxic.

In vivo, there was no increase in the incidence of chromosomal abnormalities in bone marrow cells of rats given doses of lamotrigine of up to 200 mg/kg.

Reproduction and Teratology

No evidence of teratogenicity was observed in mice, rats and rabbits given oral doses of lamotrigine at up to 14, 4 and 4 times, respectively, the currently recommended upper human maintenance dose (500 mg/gay or 7 mg/kg/day). This was true when lamotrigine was given during the period of major organogenesis or was started prior to and continued throughout the period of organogenesis. In these same oral dosing studies maternal toxicity and secondary fetal toxicity, resulting in reduced fetal weight and/or delayed ossification were seen. Teratology studies were also conducted using bolus intravenous (I.V.) administration of the isethionate salt of lamotrigine in multiples of the projected human oral dose. Intravenous lamotrigine resulted in convulsions or impaired coordination in rat and rabbit dams at 30 mg/kg and 15 mg/kg, respectively. The 30 mg/kg dose also produced an increased incidence of intrauterine death without signs of teratogenicity in rats only.

When rats were dosed prior to and during mating, and throughout gestation and lactation at daily oral doses of 5, 10 and 20 mg/kg, gestation was slightly longer in the dams allowed to deliver in the 20 mg/kg/group (22.0 ± 0.0 vs. 21.5 ± 0.5 days in non-treated controls). These doses are approximately 1, 1.5 and 3 times the currently recommended upper human maintenance dose (500 mg/kg or 7 mg/kg/day). In this same study, body weight gain and food consumption of the parent generation (F_0) dams dosed at 20 mg/kg/day were less than the control dams and were

indicative of maternal toxicity. There was no evidence of teratogenic effects in the litters of the dams designated for cesarean section. Effects secondary to maternal toxicity consisted of a decrease in mean fetal weight and length of 20 mg/kg pups, the incidence of two skeletal variants was increased and the incidence of one skeletal variant was decreased. When pregnant rats of the same strain were dosed only on days 15 to 20 of gestation at the same daily doses of 5, 10 and 20 mg/kg, more pronounced maternal toxicity than noted in the previously described study at the same doses was seen in dams given 10 and 20 mg/kg doses and consisted of dehydration, hypothermia and decreased weight gain and food consumption. A smaller decrease in body weight gain was seen in the 5 mg/kg group. Gestation was prolonged in the 20 mg/kg group (22.6 vs. 22.0 days in non-treated controls) and secondary to maternal toxicity there were increased numbers of stillborn pups (partial to entire litters) in the 10 and 20 mg/kg groups and increased early neonatal mortality.

Even at maternally toxic levels leading to fetal death, there was no evidence of teratogenicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy, only if clearly needed. Clinical data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, the effects of lamotrigine on fetal blood folate levels *in utero* are unknown.

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