Lamotrigine

Lamictal®

Lamotrigine Tablets (25, 100 and 150 mg)

THERAPEUTIC CLASS

Antiepileptic

ACTION AND CLINICAL PHARMACOLOGY

LAMICTAL (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 (e.g. glutamate, aspartate) that are thought to play a role in the generation and spread of epileptic seizures.

Clinical Trials

In placebo-controlled clinical studies, LAMICTAL 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. Studies have also been conducted using lamotrigine monotherapy in 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, percentage of patients seizure-free) with fewer side effects than currently approved therapies. Clinical trials have also demonstrated that 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 longterm treatment (up to 152 weeks).

Pharmacokinetics: Adults: LAMICTAL 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 LAMICTAL doses of 50-400 mg, peak plasma concentration (C_{max}=0.6-4.6 µg/mL) and the area under the plasma concentration-versus-time curve (AUC=29.9-211 h•µg/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, 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 ß-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine as this metabolite. **Elderly:** The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers (≥ 65 years) who each received a single oral dose of LAMICTAL (150 mg) were not different from those in healthy young volunteers. (However, see PRECAUTIONS, **Use in the Elderly**, and DOSAGE AND ADMINISTRATION.) **Renal Impairment:** The pharmacokinetics of a single oral dose of LAMICTAL (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:** The pharmacokinetics of lamotrigine in patients with impaired liver function have not been evaluated. **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 LAMICTAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine $t_{1/2}$ to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases $t_{1/2}$ and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong $t_{1/2}$ up to approximately 27 hours. Acetaminophen was shown to slightly decrease the $t_{1/2}$ and increase the clearance of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1.

Table 1: Mean Pharmacokinetic Parameters in Adult Patients with Epilepsy or Healthy Volunteers

	LAMICTAL Administered	Healthy Young Volunteers		Patients with Epilepsy		
		LAMICTAL	LAMICTAL + Valproic Acid[2]	LAMICTAL + Enzyme-Inducing AEDs	LAMICTAL + Valproic Acid	LAMICTAL + Valproic Acid + Enzyme-Inducing AEDs
T_{max} (hrs)	Single Dose	2.2 (0.25-12.0)[1]	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
$t_{1/2}$	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

ND=Not done

1 Range of individual values across studies

2 Valproic acid administered chronically (Multiple Dose Study) or for 2 days (Single Dose Study)

INDICATIONS AND CLINICAL USE

LAMICTAL (lamotrigine) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. LAMICTAL is also indicated for use as monotherapy following withdrawal of concomitant antiepileptic drugs.

CONTRAINDICATIONS

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

WARNINGS

SEVERE, POTENTIALLY LIFE-THREATENING RASHES HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THESE REPORTS, OCCURRING IN APPROXIMATELY ONE IN EVERY THOUSAND ADULTS, HAVE INCLUDED STEVENS JOHNSON SYNDROME AND, RARELY, TOXIC EPIDERMAL NECROLYSIS. RARE DEATHS HAVE BEEN REPORTED. THE INCIDENCE OF SEVERE, POTENTIALLY LIFE-THREATENING RASH IN PEDIATRIC PATIENTS APPEARS HIGHER THAN THAT REPORTED IN ADULTS USING LAMICTAL; SPECIFICALLY, REPORTS FROM CLINICAL TRIALS SUGGEST THAT AS MANY AS 1 IN 50 TO 1 IN 100 PEDIATRIC PATIENTS MAY DEVELOP A POTENTIALLY LIFE-THREATENING RASH. IT BEARS EMPHASIS, THAT LAMICTAL IS NOT CURRENTLY APPROVED FOR USE IN PATIENTS BELOW THE AGE OF 18 (see PRECAUTIONS). A HIGHER INCIDENCE OF SERIOUS DERMATOLOGIC EVENTS (see PRECAUTIONS, **Skin-related events**, TABLES 2 AND 3; see also DOSAGE AND ADMINISTRATION) HAS BEEN ASSOCIATED WITH MORE RAPID INITIAL TITRATION DOSING (EXCEEDING THE RECOMMENDED INITIAL DOSE OR EXCEEDING THE RECOMMENDED DOSE ESCALATION), AND USE OF CONCOMITANT VALPROIC ACID. NEARLY ALL CASES OF SERIOUS RASHES ASSOCIATED WITH LAMICTAL 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 SIGNALLED BY THE FIRST APPEARANCE OF A RASH. ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, 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 LAMICTAL 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. The syndrome shows a wide spectrum of clinical severity and may rarely lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and LAMICTAL discontinued if an alternative aetiology cannot be established.

Prior to initiation of treatment with LAMICTAL, 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 require a more rapid withdrawal, the dose of LAMICTAL (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 LAMICTAL does not affect them adversely. **Skin-Related Events:** In controlled studies of adjunctive lamotrigine therapy, the incidence of rash (usually maculopapular and/or erythematous) in patients receiving LAMICTAL 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 LAMICTAL. LAMICTAL was discontinued because of rash in 1.1% of 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 2 and 3; see also WARNINGS, and DOSAGE AND ADMINISTRATION.)

Table 2: Effect of Concomitant AEDs on Rash Associated with LAMICTAL in All 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
Enzyme-Inducing AEDs[1]	1,788	9.2%	1.8%	0.1%
Enzyme-Inducing AEDs[1] + VPA	318	8.8%	3.5%	0.9%
VPA ± Non-Enzyme-Inducing AEDs[2]	159	20.8%	11.9%	2.5%
Non-Enzyme-Inducing AEDs[2]	27	18.5%	0.0%	0.0%

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

2 Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin

Table 3: Effect of the Initial Daily Dose[1] of LAMICTAL in the Presence of Concomitant AEDs, on the Incidence of Rash Leading to Withdrawal of Treatment in Add-On Clinical Trials

AED Group	Enzyme-Inducing AEDs[2]		Enzyme-Inducing AEDs[2] + VPA		VPA ± Non-Enzyme-Inducing AEDs[3]	
LAMICTAL Average Daily Dose (mg)	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients Withdrawn
12.5	9	0.0	10	0.0	51	7.8
25	3	0.0	7	0.0	58	12.1
50	182	1.1	111	0.9	35	5.7
100	993	1.4	179	4.5	15	40.0
≥ 125	601	2.8	11	18.2	0	0.0

1 Average daily dose in week 1

2 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

3 Non-enzyme-inducing AEDs 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, 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 LAMICTAL 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 LAMICTAL did not affect the plasma concentration of valproic acid in patients receiving enzyme-inducing AEDs in combination with valproic acid. (See also PRECAUTIONS, **Skin-Related Events.**) **Oral Contraceptives:** In a study of 12 female volunteers, LAMICTAL 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**). **Drug/Laboratory Test Interactions:** LAMICTAL has not been associated with any assay interferences in clinical laboratory tests. **Use in the Elderly:** The safety and efficacy of LAMICTAL in elderly patients with epilepsy have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions and limited experience with LAMICTAL in this population. **Use in Children:** The safety and efficacy of LAMICTAL in children under 18 years of age have not yet been established (see WARNINGS). **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, LAMICTAL should only be used during pregnancy if the benefits of therapy outweigh the risks associated with it. Clinical trials data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, its effects during human fetal development are unknown. **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is unknown. **Nursing Mothers:** LAMICTAL is excreted in human milk. Because of the potential for adverse reactions from LAMICTAL in nursing infants, breast-feeding while taking this medication is not recommended. **Patients with Special Diseases and Conditions:** Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL 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 LAMICTAL in patients with severe renal impairment should proceed with caution. **Impaired Liver Function:** There is no experience with the use of LAMICTAL in patients with impaired liver function. Caution should be exercised in dose selection for patients with this condition. **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 LAMICTAL 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, LAMICTAL 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 LAMICTAL, nor is there evidence of psychological or physical dependence in humans. **Laboratory Tests:** The use of LAMICTAL 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. THE LATTER CONDITION CARRIES A HIGH MORTALITY (see WARNINGS). Adverse experiences in patients receiving LAMICTAL (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 LAMICTAL (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 LAMICTAL than in patients receiving other enzyme-inducing AEDs with LAMICTAL. Reduction of the daily dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or LAMICTAL may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic

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acid, or non-inducing AEDs (see WARNINGS; see also PRECAUTIONS, **Skin-Related Events,** Table 2). **Adverse Events Associated with Discontinuation of Treatment:** Across all add-on studies, the most common adverse experiences associated with discontinuation of LAMICTAL 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 LAMICTAL discontinued therapy due to an adverse experience, versus 2.9% of the 419 patients receiving placebo. Of 3,501 patients and volunteers who received LAMICTAL in premarketing 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 patients and volunteers who received LAMICTAL in the premarketing studies. Rash accounted for almost half of the discontinuations due to serious adverse experiences. More rapid initial titration dosing of LAMICTAL, and concomitant use of valproic acid were associated with higher incidences of rash-related withdrawal in clinical studies (see WARNINGS; see also PRECAUTIONS, **Skin-Related Events,** Table 3). **Controlled Add-on Clinical Studies:** Table 4 enumerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with LAMICTAL. **Other Events Observed During Clinical Studies:** During clinical testing, multiple doses of LAMICTAL were administered to 3,501 patients and volunteers. The conditions and duration of exposure to LAMICTAL 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 LAMICTAL 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 LAMICTAL in combination with other antiepileptic drugs, they were not necessarily caused by LAMICTAL. The following adverse events have been reported on one or more occasions by at least 1% of patients and volunteers exposed to LAMICTAL: 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 4.)

Table 4: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Studies[1]

Body System / Adverse Experience[2]	Percent of Patients Receiving LAMICTAL (and other AEDs) (n=711)	Percent of Patients Receiving Placebo (and other AEDs) (n=419)	Percent of Patients Receiving LAMICTAL (and other AEDs) Who Were Discontinued (n=711)
BODY AS A WHOLE			
Headache	29.1	19.1	1.3
Accidental Injury	9.1	8.6	0.1
Asthenia	8.6	8.8	0.3
Flu Syndrome	7.0	5.5	0.0
Pain	6.2	2.9	0.1
Back Pain	5.8	6.2	0.0
Fever	5.5	3.6	0.1
Abdominal Pain	5.2	3.6	0.1
Infection	4.4	4.1	0.0
Neck Pain	2.4	1.2	0.0
Malaise	2.3	1.9	0.3
Seizure Exacerbation	2.3	0.5	0.3
DIGESTIVE			
Nausea	18.6	9.5	1.3
Vomiting	9.4	4.3	0.3
Diarrhea	6.3	4.1	0.3
Dyspepsia	5.3	2.1	0.1
Constipation	4.1	3.1	0.0
Tooth Disorder	3.2	1.7	0.0
MUSCULOSKELETAL			
Myalgia	2.8	3.1	0.0
Arthralgia	2.0	0.2	0.0
NERVOUS			
Dizziness	38.4	13.4	2.4
Ataxia	21.7	5.5	0.6
Somnolence	14.2	6.9	0.0
Incoordination	6.0	2.1	0.3
Insomnia	5.6	1.9	0.4
Tremor	4.4	1.4	0.0
Depression	4.2	2.6	0.0
Anxiety	3.8	2.6	0.0
Convulsion	3.2	1.2	0.3
Irritability	3.0	1.9	0.1
Speech Disorder	2.5	0.2	0.1
Memory Decreased	2.4	1.9	0.0
RESPIRATORY			
Rhinitis	13.6	9.3	0.0
Pharyngitis	9.8	8.8	0.0
Cough Increased	7.5	5.7	0.0
Respiratory Disorder	5.3	5.5	0.1
SKIN AND APPENDAGES			
Rash	10.0	5.0	1.1
Pruritus	3.1	1.7	0.3
SPECIAL SENSES			
Diplopia	27.6	6.7	0.7
Blurred Vision	15.5	4.5	1.1
Vision Abnormality	3.4	1.0	0.0
UROGENITAL			
Female Patients	**(n=365)**	**(n=207)**	
Dysmenorrhea	6.6	6.3	0.0
Menstrual Disorder	5.2	5.8	0.0
Vaginitis	4.1	0.5	0.0

1 Patients in these studies were receiving 1 to 3 concomitant enzyme-inducing antiepileptic drugs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation. Thus, patients may be included in more than one category.

2 Adverse Experiences reported by at least 2% of patients treated with LAMICTAL are included.

Monotherapy Clinical Studies: Withdrawals due to adverse events were reported in 42 (9.5%) of newly diagnosed patients treated with LAMICTAL monotherapy. The most common adverse experiences associated with discontinuation of LAMICTAL were rash (6.1%), asthenia (1.1%), headache (1.1%), nausea (0.7%) and vomiting (0.7%). **Other Events Observed During Clinical Practice and from "Compassionate Plea" Patients:** In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving LAMICTAL marketed in other countries and from worldwide "compassionate plea" patients. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: apnea, erythema multiforme, esophagitis, hematemesis, hemolytic anemia, pancreatitis, pancytopenia and progressive immunosuppression.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

During the clinical development program, the highest known overdose of LAMICTAL (lamotrigine) occurred in a 33-year old female who ingested between 4,000 and 5,000 mg LAMICTAL that corresponded to a plasma level of 52 µg/mL four hours after the ingestion. The patient presented to the emergency room comatose and remained comatose for 8 to 12 hours, returned to almost normal over the next 24 hours, and completely recovered by the third day. There are no specific antidotes for LAMICTAL. 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

Adults: LAMICTAL (lamotrigine) is intended for oral administration and may be taken with or without food. LAMICTAL 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 LAMICTAL as summarized in Table 5. LAMICTAL 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 LAMICTAL 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 LAMICTAL, a step-wise reduction of dose over at least two weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal (see PRECAUTIONS). The relationship of plasma concentration to clinical response has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response. In controlled clinical studies, doses of LAMICTAL 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 LAMICTAL producing this plasma concentration range were well tolerated. As with any antiepileptic drug, the oral dose of LAMICTAL should be adjusted to the needs of the individual patient, taking into consideration the concomitant AED therapy the patient is receiving.

Table 5: LAMICTAL Recommended Dosage Schedule for Adults

Treatment Week	Patients Taking		For Information*
	Enzyme-Inducing AEDs[1] *With* Valproic Acid	Enzyme-Inducing AEDs[1] *Without* Valproic Acid	Patients Taking Valproic Acid *Only*
Weeks 1 + 2	25 mg once a day	50 mg once a day	25 mg every other day
Weeks 3 + 4	25 mg twice a day	50 mg twice a day	25 mg once a day
Usual Maintenance	50-100 mg twice a day To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks.	150-250 mg twice a day To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks.	50-100 mg twice a day To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks.

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

* Column reflects dosage recommendations in the United Kingdom and is provided for information.

Because of an increased risk of rash, the recommended initial dose and subsequent dose escalations of LAMICTAL should not be exceeded (see WARNINGS).

There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the addition of LAMICTAL 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, Table 3; see also WARNINGS). The potential medical benefits of addition of LAMICTAL under these conditions must be weighed against the increased risk of serious rash. If use of LAMICTAL under these conditions is considered clinically indicated, titration dosing should proceed with extreme caution, especially during the first six weeks of treatment.

Withdrawal of Concomitant AEDs: 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 LAMICTAL 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 LAMICTAL. 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 LAMICTAL. **Geriatric Patients:** There is little experience with the use of LAMICTAL in elderly patients. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions. **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:** There is no experience with the use of LAMICTAL in patients with impaired liver function. Because lamotrigine is metabolized by the liver, caution should be exercised in dose selection for patients with this condition. **Children:** Dosage recommendations for children under 18 years of age are not yet established.

PHARMACEUTICAL INFORMATION

Drug Substance

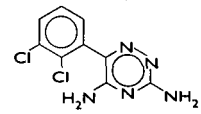
Brand Name: LAMICTAL

Common Name: Lamotrigine

Chemical Name: 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-[USAN]

Chemical Name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine [Chem. Abstr.]

Structural Formula: [USAN]



Molecular Formula: $C_9H_7Cl_2N_5$ Molecular Weight: 256.09

Description: Lamotrigine is a white to pale cream powder. The pKa at 25°C is 5.7. It is practically insoluble in water (0.017% w/v); slightly soluble in ethanol (0.41% w/v), chloroform (0.11% w/v) and octanol (0.28% w/v).

Composition

LAMICTAL Tablets contain lamotrigine and the following non-medicinal ingredients: cellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and coloring agents:

- 25 mg (white tablets) - None
- 100 mg (peach tablets) - Sunset Yellow FCF Lake
- 150 mg (cream tablets) - Ferric Oxide, Yellow

Stability and Storage Recommendations

LAMICTAL Tablets should be stored at controlled room temperature (15°C to 30°C) in a dry place and protected from light.

AVAILABILITY OF DOSAGE FORMS

LAMICTAL Tablets are available in three different strengths:

- LAMICTAL Tablets 25 mg: White, scored, shield-shaped tablets engraved with "LAMICTAL" and "25". Bottles of 100.
- LAMICTAL Tablets 100 mg: Peach, scored, shield-shaped tablets engraved with "LAMICTAL" and "100". Bottles of 100.
- LAMICTAL Tablets 150 mg: Cream, scored, shield-shaped tablets engraved with "LAMICTAL" and "150". Bottles of 60.

Product Monograph available to healthcare professionals on request.

Date of revision: April 16, 1997

References: 1. Schmidt D & Gram L. Monotherapy versus polytherapy in epilepsy. *CNS Drugs* 1995; 3:194-208. **2.** Brodie MJ. Lamotrigine - An update. *Can J Neurol Sci* 1996; 23(Suppl. 2):S6-S9. **3.** Product Monograph of LAMICTAL (lamotrigine), Glaxo Wellcome Inc. 1997. **4.** Faught E. Lamotrigine monotherapy in patients with refractory partial-onset seizures. *In:* Loiseau P (ed.) *Lamotrigine - A Brighter Future. International Congress and Symposium Series 214.* London: The Royal Society of Medicine Press; 1996:37-42. **5.** Perucca E. Add-on trial of lamotrigine followed by withdrawal of concomitant medication and stabilization on monotherapy. *In:* Loiseau P (ed.) *Lamotrigine - A Brighter Future. International Congress and Symposium Series 214.* London: The Royal Society of Medicine Press; 1996:23-30. **6.** Brodie MJ. Lamotrigine monotherapy: an overview. *In:* Loiseau P (ed.) *Lamotrigine – A Brighter Future. International Congress and Symposium Series 214.* London: The Royal Society of Medicine Press; 1996:43-49.

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