

LIMBITROL® C^{IV}

(chlordiazepoxide)

(amitriptyline HCl)

DS (double strength) TABLETS

TABLETS

Tranquilizer – Antidepressant

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see *Warnings, Drug-Drug Interactions*].

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Chlordiazepoxide and Amitriptyline Hydrochloride Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in the risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LIMBITROL is not approved for use in pediatric patients. (See **Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric**

DESCRIPTION: LIMBITROL combines for oral administration, chlordiazepoxide, an agent for the relief of anxiety and tension, and amitriptyline, an antidepressant. It is

available in DS (double strength) white, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt); and in blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Each tablet also contains corn starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone and propylene glycol; LIMBITROL tablets contain the following colorant system-FD&C Blue No. 1, aluminum lake and titanium dioxide. LIMBITROL DS tablets contain titanium dioxide.

Chlordiazepoxide is a benzodiazepine with the formula 7-chloro-2-(methyl-amino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide. It is a slightly yellow crystalline material and is insoluble in water. The molecular weight is 299.76.

Amitriptyline is a dibenzocycloheptadiene derivative. The formula is 10,11-dihydro-*N,N*-dimethyl-5H-dibenzo [a,d] cycloheptene- Δ^5 -propylamine hydrochloride. It is a white or practically white crystalline compound that is freely soluble in water. The molecular weight is 313.87.

ACTIONS: Both components of LIMBITROL exert their action in the central nervous system. Extensive studies with chlordiazepoxide in many animal species suggest action in the limbic system. Recent evidence indicates that the limbic system is involved in emotional response. Taming action was observed in some species. The mechanism of action of amitriptyline in man is not known, but the drug appears to interfere with the reuptake of norepinephrine into adrenergic nerve endings. This action may prolong the sympathetic activity of biogenic amines.

INDICATIONS: LIMBITROL is indicated for the treatment of patients with moderate to severe depression associated with moderate to severe anxiety.

The therapeutic response to LIMBITROL occurs earlier and with fewer treatment failures than when either amitriptyline or chlordiazepoxide is used alone.

Symptoms likely to respond in the first week of treatment include: insomnia, feelings of guilt or worthlessness, agitation, psychic and somatic anxiety, suicidal ideation and anorexia.

CONTRAINDICATIONS: LIMBITROL is contraindicated in patients with hypersensitivity to either benzodiazepines or tricyclic antidepressants. It should not be given concomitantly with a monoamine oxidase inhibitor. Hyperpyretic crises, severe convulsions and deaths have occurred in patients receiving a tricyclic antidepressant and a monoamine oxidase inhibitor simultaneously. When it is desired to replace a monoamine oxidase inhibitor with LIMBITROL, a minimum of 14 days should be allowed to elapse after the former is discontinued. LIMBITROL should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

This drug is contraindicated during the acute recovery phase following myocardial infarction.

WARNINGS:

Risks from Concomitant Use with Opioids: Concomitant use of benzodiazepines, including Limbitrol, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Limbitrol concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Limbitrol than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking Limbitrol, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Limbitrol is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined. [see Drug Interactions].

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but the tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

	Drug-Related Increases
< 18	14 additional cases
18-24	5 additional cases
	Drug Related Decreases
25-64	1 fewer cases
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All pediatric patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LIMBITROL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is

unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that LIMBITROL is not approved for use in treating bipolar depression.

General: Because of the atropine-like action of the amitriptyline component, great care should be used in treating patients with a history of urinary retention or angle-closure glaucoma. In patients with glaucoma, even average doses may precipitate an attack. Severe constipation may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia and prolongation of conduction time. Myocardial infarction and stroke have been reported in patients receiving drugs of this class.

Because of the sedative effects of LIMBITROL, patients should be cautioned about combined effects with alcohol or other CNS depressants. The additive effects may produce a harmful level of sedation and CNS depression.

Patients receiving LIMBITROL should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Usage in Pregnancy: Safe use of LIMBITROL during pregnancy and lactation has not been established. Because of the chlordiazepoxide component, please note the following:

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE section.)

PRECAUTIONS: General: Use with caution in patients with a history of seizures.

Close supervision is required when LIMBITROL is given to hyperthyroid patients or those on thyroid medication.

The usual precautions should be observed when treating patients with impaired renal or hepatic function.

Patients with suicidal ideation should not have easy access to large quantities of the drug. The possibility of suicide in depressed patients remains until significant remission occurs.

Essential Laboratory Tests: Patients on prolonged treatment should have periodic liver function tests and blood counts.

Drug-Drug Interactions

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA_A sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Topiramate

Some patients may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

Drug and Treatment Interactions: Because of its amitriptyline component, LIMBITROL may block the antihypertensive action of guanethidine or compounds with a similar mechanism of action.

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7% to 10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the type 1c antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

The effects of concomitant administration of LIMBITROL and other psychotropic drugs have not been evaluated. Sedative effects may be additive.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants and benzodiazepines, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine (Tagamet).

The drug should be discontinued several days before elective surgery.

Concurrent administration of ECT and LIMBITROL should be limited to those patients for whom it is essential.

Pregnancy: See WARNINGS section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug, since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS-*Clinical Worsening and Suicide Risk*).

Anyone considering the use of Chlordiazepoxide and Amitriptyline Hydrochloride Tablets in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: In elderly and debilitated patients it is recommended that dosage be limited to the smallest effective amount to preclude the development of ataxia, oversedation, confusion or anticholinergic effects.

Of the total number of subjects in clinical studies of LIMBITROL, 74 individuals were 65 years and older. An additional 34 subjects were between 60 and 69 years of age. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The active ingredients in LIMBITROL are known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of LIMBITROL and observed closely.

Clinical studies of LIMBITROL did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with LIMBITROL and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for LIMBITROL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking LIMBITROL.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS: Adverse reactions to LIMBITROL are those associated with the use of either component alone. Most frequently reported were drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Other side effects occurring less commonly included vivid dreams, impotence, tremor, confusion and nasal congestion. Many symptoms common to the depressive state, such as anorexia, fatigue, weakness, restlessness and lethargy, have been reported as side effects of treatment with both LIMBITROL and amitriptyline.

Granulocytopenia, jaundice and hepatic dysfunction of uncertain etiology have also been observed rarely with LIMBITROL. When treatment with LIMBITROL is prolonged, periodic blood counts and liver function tests are advisable.

Note: Included in the listing which follows are adverse reactions which have not been reported with LIMBITROL. However, they are included because they have been reported during therapy with one or both of the components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations,

hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

DRUG ABUSE AND DEPENDENCE: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of chlordiazepoxide. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Withdrawal symptoms (e.g., nausea, headache and malaise) have also been reported in association with abrupt amitriptyline discontinuation. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving chlordiazepoxide or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE*: Deaths may occur from overdose with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations: Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia or any of the symptoms listed under

ADVERSE REACTIONS.

Management: General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. ***There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination.*** Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalization, to a pH of 7.45 to 7.56, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a pCO₂ < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type ***IA and IC*** antiarrhythmics are generally contraindicated (eg, quinidine, disopyramide and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). ***Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies,*** and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdoses are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

*Poisindex[®] Toxicologic Management. Topic: Antidepressants, Tricyclic.

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Chlordiazepoxide Overdosage: Manifestations of benzodiazepine overdose include somnolence, confusion, coma and diminished reflexes. Dialysis is of limited value. There have been occasional reports of excitation in patients following benzodiazepine

overdosage; if this occurs, barbiturates should not be used. Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section). Since LIMBITROL contains amitriptyline, it is important to note that use of the benzodiazepine antagonist flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

DOSAGE AND ADMINISTRATION: Optimum dosage varies with the severity of the symptoms and the response of the individual patient. When a satisfactory response is obtained, dosage should be reduced to the smallest amount needed to maintain the remission. The larger portion of the total daily dose may be taken at bedtime. In some patients, a single dose at bedtime may be sufficient. In general, lower dosages are recommended for elderly patients.

LIMBITROL DS (double strength) Tablets are recommended in an initial dosage of 3 or 4 tablets daily in divided doses; this may be increased to 6 tablets daily as required. Some patients respond to smaller doses and can be maintained on 2 tablets daily.

LIMBITROL Tablets in an initial dosage of 3 or 4 tablets daily in divided doses may be satisfactory in patients who do not tolerate higher doses.

HOW SUPPLIED: *LIMBITROL DS (double strength) Tablets* are available as white, film-coated, biconvex tablets containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) in bottles of 100 (NDC 23155-562-01). Each tablet is engraved “V 3806” on one side.

LIMBITROL Tablets are available as blue, film-coated, biconvex tablets containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) in bottles of 100 (NDC 23155-563-01). Each tablet is engraved “V 3805” on one side.

Store at 20° to 25°C (68° to 77°F). [See USP controlled room temperature.] Store in a dry place. Keep in a tightly closed, child-resistant container and out of the light.

Manufactured for:

Heritage Pharmaceuticals Inc.

Eatontown, NJ 07724

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MEDICATION GUIDE

Limbitrol (LIM-bi-trol)

(chlordiazepoxide and amitriptyline hydrochloride) Tablets, C-IV

What is the most important information I should know about Limbitrol?

- **This medicine contains chlordiazepoxide. Chlordiazepoxide is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- **Suicidal thoughts or actions.** Limbitrol and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults (18 to 24 years of age) **within the first few months of treatment or when the dose is changed.**
- **Depression or other serious mental illnesses are the most important cause of suicidal thoughts or actions.**
- **How can I watch for and try to prevent suicidal thoughts and actions?**
 - Pay particular attention to such changes when Limbitrol is started or when the dose is changed.
 - Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.
 - **Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:**
 - attempts to commit suicide
 - acting on dangerous impulses
 - acting aggressive or violent
 - thoughts about suicide or dying
 - new or worse depression
 - new or worse anxiety or panic attacks
 - feeling agitated, restless, angry or irritable
 - trouble sleeping (insomnia)
 - an increase in activity or talking more than what is normal for you (mania)
 - other unusual changes in behavior or mood
- **Limbitrol can make you sleepy or dizzy, and can slow your thinking and motor skills.**
 - Do not drive, operate heavy machinery, or do other dangerous activities until you know how Limbitrol affects you.
 - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking Limbitrol without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, Limbitrol may make your sleepiness or dizziness much worse.
- Do not take more Limbitrol than prescribed.

What is Limbitrol?

- Limbitrol is a prescription medicine used to treat moderate to severe depression that can happen with moderate to severe anxiety.
- **Limbitrol is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep Limbitrol in a safe place to prevent misuse and abuse. Selling or giving away Limbitrol may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if Limbitrol is safe and effective in children.

Do not take Limbitrol if you:

- are allergic to benzodiazepines or tricyclic antidepressant medicines
- take a medicine called a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
- are recovering from a heart attack (myocardial infarction)

Before you take Limbitrol, tell your healthcare provider about all of your medical conditions, including if you:

- have bipolar disorder (manic depression) or mania
- have a history of drug or alcohol abuse or addiction
- have eye problems
- have problems urinating or emptying your bladder
- have kidney or liver problems
- have or had heart problems, including heart attack or a stroke
- have or have had seizures
- have a thyroid problem
- plan to have surgery
- receive electroconvulsive therapy (ECT)
- are pregnant or plan to become pregnant. Limbitrol may harm your unborn baby. Avoid taking Limbitrol during the first trimester of pregnancy. Tell your healthcare provider right away if you become pregnant during treatment with Limbitrol.
- are breastfeeding or plan to breastfeed. It is not known if Limbitrol passes into your breast milk. You should not breastfeed while taking Limbitrol. Talk to your healthcare provider about the best way to feed our baby if you take Limbitrol.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking Limbitrol with certain other medicines can cause side effects or affect how well Limbitrol or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take Limbitrol?

- Take Limbitrol exactly as your healthcare provider tells you to take it.
- If you take too much Limbitrol, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of Limbitrol?

Limbitrol may cause serious side effects, including:

- See **“What is the most important information I should know about Limbitrol?”**
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking Limbitrol suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping Limbitrol to avoid withdrawal symptoms.
- **Abuse and dependence.** Taking Limbitrol can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.

The most common side effects of Limbitrol include:

- drowsiness
- constipation
- dizziness

- dry mouth
- blurred vision
- bloating

These are not all the possible side effects of Limbitrol. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Limbitrol?

- Store at 20° to 25°C (68° to 77°F). [See USP controlled room temperature.] Store in a dry place.
- Keep Limbitrol in a tightly closed, child-resistant container and out of the light.
- **Keep Limbitrol and all medicines out of the reach of children.**

General information about the safe and effective use of Limbitrol.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Limbitrol for a condition for which it was not prescribed. Do not give Limbitrol to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Limbitrol that is written for health professionals.

What are the ingredients in Limbitrol tablets?

Active ingredient: clordiazepoxide, amitriptyline (as the hydrochloride salt)

Inactive ingredients: corn starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone and propylene glycol;

LIMBITROL tablets contain the following colorant system-FD&C Blue No. 1, aluminum lake and titanium dioxide. LIMBITROL DS tablets contain titanium dioxide.

Manufactured for: **Heritage Pharmaceuticals Inc.**, Eatontown, NJ 07724

For more information, go to www.heritagepharma.com or call 1.866.901.DRUG (3784)

This medication Guide has been approved by the U.S. Food and Drug Administration.

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