

**CHLORDIAZEPOXIDE
and
AMITRIPTYLINE HYDROCHLORIDE
TABLETS, USP**

5 mg/12.5 mg and 10 mg/25 mg

R only

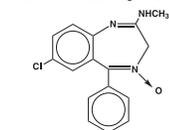


Suicidal and Antidepressant Drugs

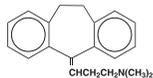
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of chlordiazepoxide and amitriptyline or 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 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. Chlordiazepoxide and amitriptyline is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRECAUTIONS: Pediatric Use.)

DESCRIPTION: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP combine for oral administration, chlordiazepoxide, an agent for the relief of anxiety and tension, and amitriptyline, an antidepressant.

Chlordiazepoxide, USP is a benzodiazepine with the formula 7-chloro-2-(methylamino)-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. Its structural formula is:



Amitriptyline, USP is a dibenzocycloheptadiene derivative. The formula is 10,11-dihydro-*N,N*-dimethyl-5H-dibenzo[*a,d*]cycloheptene-5,7- γ -propylamine hydrochloride. It is a white or practically white crystalline compound that is freely soluble in water. The molecular weight is 313.87. Its structural formula is:



Each tablet for oral administration contains:

5 mg of chlordiazepoxide and 12.5 mg of amitriptyline (as the hydrochloride salt) or

10 mg of chlordiazepoxide and 25 mg of amitriptyline (as the hydrochloride salt) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch (corn), sodium lauryl sulfate, and titanium dioxide.

In addition, the 5 mg/12.5 mg product contains D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake and the 10 mg/25 mg product contains calcium sulfate and talc.

CLINICAL PHARMACOLOGY: Both components of Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP 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 AND USAGE: Chlordiazepoxide and amitriptyline hydrochloride is indicated for the treatment of patients with moderate to severe depression associated with moderate to severe anxiety.

The therapeutic response to chlordiazepoxide and amitriptyline hydrochloride 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: Chlordiazepoxide and amitriptyline hydrochloride is contraindicated in patients with hypersensitivity to either benzodiazepines or tricyclic antidepressants. It should not be given concomitantly with a monoamine oxidase inhibitor. Hypertensive 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 chlordiazepoxide and amitriptyline hydrochloride, a minimum of 14 days should be allowed to elapse after the former is discontinued. Chlordiazepoxide and amitriptyline hydrochloride 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: 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 to 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 4,400 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 a 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 1,000 patients treated) are provided in Table 1.

Table 1	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality Per 1,000 Patients Treated
Increases Compared to Placebo	
< 18	14 additional cases
18 to 24	5 additional cases
Decreases Compared to Placebo	
25 to 64	1 fewer case
≥ 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 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 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 chlordiazepoxide and amitriptyline 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 chlordiazepoxide and amitriptyline is not approved for use in treating bipolar depression.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including chlordiazepoxide and amitriptyline hydrochloride may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

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 chlordiazepoxide and amitriptyline hydrochloride, 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 chlordiazepoxide and amitriptyline hydrochloride 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 chlordiazepoxide and amitriptyline hydrochloride 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 discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE.)

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

Close supervision is required when chlordiazepoxide and amitriptyline hydrochloride 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.

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 chlordiazepoxide and amitriptyline 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 chlordiazepoxide and amitriptyline. 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 chlordiazepoxide and amitriptyline.

Patients should be advised that taking chlordiazepoxide and amitriptyline hydrochloride can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

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.

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

Drug and Treatment Interactions: Because of its amitriptyline component, chlordiazepoxide and amitriptyline hydrochloride 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 all 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 chlordiazepoxide and amitriptyline hydrochloride 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.

The drug should be discontinued several days before elective surgery.

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

Pregnancy: See WARNINGS.

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 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, over sedation, confusion or anticholinergic effects.

Of the total number of subjects in clinical studies of chlordiazepoxide and amitriptyline hydrochloride tablets, 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 chlordiazepoxide and amitriptyline hydrochloride tablets 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 chlordiazepoxide and amitriptyline hydrochloride tablets and observed closely.

Clinical studies of chlordiazepoxide and amitriptyline hydrochloride tablets 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.

ADVERSE REACTIONS: Adverse reactions to chlordiazepoxide and amitriptyline hydrochloride 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 chloridiazepoxide and amitriptyline hydrochloride tablets and amitriptyline tablets.

Granulocytopenia, jaundice and hepatic dysfunction of uncertain etiology have also been observed rarely with chloridiazepoxide and amitriptyline hydrochloride. When treatment with chloridiazepoxide and amitriptyline hydrochloride 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 chloridiazepoxide and amitriptyline hydrochloride. 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 gynecostasia 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 chloridiazepoxide. 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 (e.g., 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 discontinuance. Consequently, after extended therapy, abrupt discontinuance 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 chloridiazepoxide or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE: Deaths may occur from overdosage 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, hyperthermia, 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 $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., 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.

*Poisondex® Toxicologic Management. Topic: Antidepressants, Tricyclic. Micromedex Inc. Vol. 85.

Chloridiazepoxide Overdosage: Manifestations of benzodiazepine overdosage 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). Since chloridiazepoxide and amitriptyline hydrochloride 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.

DOSE 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.

Chloridiazepoxide and Amitriptyline Hydrochloride Tablets, USP 10 mg/25 mg 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.

Chloridiazepoxide and Amitriptyline Hydrochloride Tablets, USP 5 mg/12.5 mg 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: Chloridiazepoxide and Amitriptyline Hydrochloride Tablets, USP are available containing 5 mg of chloridiazepoxide, USP and 12.5 mg of amitriptyline, USP (as the hydrochloride salt) or 10 mg of chloridiazepoxide, USP and 25 mg of amitriptyline, USP (as the hydrochloride salt).

The 5 mg/12.5 mg tablets are green film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **211** on the other side. They are available as follows:

NDC 0378-0211-01
bottles of 100 tablets
NDC 0378-0211-05
bottles of 500 tablets

The 10 mg/25 mg tablets are white film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **277** on the other side. They are available as follows:

NDC 0378-0277-01
bottles of 100 tablets
NDC 0378-0277-05
bottles of 500 tablets

Store at 20° to 25°C (68° to 77°F). (See USP for Controlled Room Temperature.)

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.



Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

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Medication Guide

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especial-

ly if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
- **visual problems:** eye pain, changes in vision, swelling or redness in or around the eye.

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Visual problems:** Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Revised 5/2014