PERPHENAZINE and AMITRIPTYLINE HYDROCHLORIDE TABLETS, USP

2 mg/10 mg, 2 mg/25 mg, 4 mg/10 mg, 4 mg/25 mg and 4 mg/50 mg

℞ only

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Perphenazine and amitriptyline hydrochloride is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

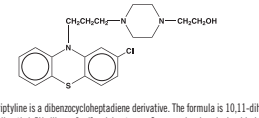
Suicidality and Antidepressant Drugs

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 perphenazine 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. Perphenazine and amitriptyline hydrochloride is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRECAUTIONS: Pediatric Use.)

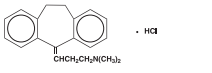
PRAT:R16mc

DESCRIPTION: Perphenazine and amitriptyline hydrochloride, a broad spectrum psychotherapeutic agent for the management of outpatients and hospitalized patients with psychoses or neuroses characterized by mixtures of anxiety or agitation with symptoms of depression, is a combination of perphenazine and amitriptyline hydrochloride. Since such mixed syndromes can occur in patients with various degrees of intensity of mental illness, perphenazine and amitriptyline hydrochloride tablets are provided in multiple combinations to afford dosage flexibility for optimum management.

Perphenazine is a phenothiazine derivative. The formula is 4-[3-(2-chloro-10*H*-phenothiazin-10yl) propyl]-piperazineethanol. Perphenazine, USP is a white, odorless, bitter tasting powder that is insoluble in water. The molecular weight is 403.97. Its structural formula is:



Amitriptyline is a dibenzocycloheptadiene derivative. The formula is 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[a,d]cycloheptene-Δ^{5},γ-propylamine hydrochloride. Amitriptyline hydrochloride, USP is a white, odorless, crystalline compound which is freely soluble in water. The molecular weight is 313.87. Its structural formula is:



Each tablet for oral administration contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch (corn), sodium lauryl sulfate and titanium dioxide.

The following additional product specific inactive ingredients are employed:

- 2 mg/10 mg - hydroxypropyl cellulose
- 2 mg/25 mg - hydroxypropyl cellulose
- 4 mg/10 mg - polysorbate 80
- 4 mg/25 mg - hydroxypropyl cellulose
- 4 mg/50 mg - hydroxypropyl cellulose

The following product specific coloring agents are employed:

- 2 mg/10 mg - calcium sulfate, talc
- 2 mg/25 mg - D&C Red No. 7 Calcium Lake, FD&C Blue No. 1 Aluminum Lake
- 4 mg/10 mg - FD&C Blue No. 1 Aluminum Lake
- 4 mg/25 mg - FD&C Yellow No. 6 Aluminum Lake
- 4 mg/50 mg - D&C Red No. 7 Calcium Lake, FD&C Blue No. 1 Aluminum Lake

CLINICAL PHARMACOLOGY: Perphenazine: In common with all members of the piperazine group of phenothiazine derivatives, perphenazine has greater behavioral potency than phenothiazine derivatives of other groups without a corresponding increase in autonomic, hematologic, or hepatic side effects.

Extrapyramidal effects, however, may occur more frequently. These effects are interpreted as neuropharmacologic. They usually regress after discontinuation of the drug.

Perphenazine is a potent tranquilizer and also a potent antiemetic. Orally, its milligram potency is about 5 or 6 times that of chlorpromazine with respect to behavioral effects. It is capable of alleviating symptoms of anxiety, tension, psychomotor excitement, and other manifestations of emotional stress without apparent dulling of mental acuity.

Amitriptyline Hydrochloride: Amitriptyline hydrochloride is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

INDICATIONS AND USAGE: Perphenazine and amitriptyline hydrochloride tablets are recommended for treatment of (1) patients with **moderate to severe anxiety and/or agitation and depressed mood,** (2) patients with **depression in whom anxiety and/or agitation are severe,** and (3) patients with **depression and anxiety in association with chronic physical disease.** In many of these patients, anxiety masks the depressive state so that, although therapy with a tranquilizer appears to be indicated, the administration of a tranquilizer alone will not be adequate.

Schizophrenic patients who have associated depressive symptoms should be considered for therapy with perphenazine and amitriptyline hydrochloride tablets.

CONTRAINDICATIONS: Perphenazine and amitriptyline hydrochloride tablets are contraindicated in depression of the central nervous system from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); in the presence of evidence of bone marrow depression; and in patients known to be hypersensitive to phenothiazines or amitriptyline.

It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. When it is desired to replace a monoamine oxidase inhibitor with perphenazine and amitriptyline hydrochloride, a minimum of 14 days should be allowed to elapse after the former is discontinued. Perphenazine and amitriptyline hydrochloride should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Amitriptyline hydrochloride is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Perphenazine and amitriptyline hydrochloride is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).

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 nine 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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for perphenazine and amitriptyline hydrochloride 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 perphenazine and amitriptyline hydrochloride is not approved for use in treating bipolar depression.

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

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

General: Perphenazine and amitriptyline hydrochloride should not be given concomitantly with guanethidine or similarly acting compounds, since amitriptyline, like other tricyclic antidepressants, may block the antihypertensive effect of these compounds.

Because of the atropine like activity of amitriptyline, this product should be used with caution in patients with a history of urinary retention, or with angle-closure glaucoma. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

It should be used with caution also in patients with convulsive disorders. Dosage of anticonvulsive agents may have to be increased.

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

Close supervision is required when amitriptyline hydrochloride is given to hyperthyroid patients or those receiving thyroid medication.

This product may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Usage in Pregnancy: Perphenazine and amitriptyline hydrochloride is not recommended for use in pregnant patients or in nursing mothers at this time. Reproduction studies in rats have shown no fetal abnormalities; however, clinical experience and follow-up in pregnancy have been limited, and the possibility of adverse effects on fetal development must be considered.

Pregnancy: ***Nonteratogenic Effects:*** Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Perphenazine and amitriptyline hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PRECAUTIONS: General: The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: As with all phenothiazine compounds, perphenazine should not be used indiscriminately. Caution should be observed in giving it to patients who have previously exhibited severe adverse reactions to other phenothiazines.

Some of the untoward actions of perphenazine tend to appear more frequently when high doses are used. However, as with other phenothiazine compounds, patients receiving perphenazine in any dosage should be kept under close supervision.

The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs, or render more difficult the diagnosis of disorders such as brain tumors or intestinal obstruction.

A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case this product should be discontinued.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Amitriptyline Hydrochloride: Depressed patients, particularly those with known manic depressive illness, may experience a shift to mania or hypomania. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of this product seems to reduce the likelihood of these effects.

Both elevation and lowering of blood sugar levels have been reported.

Amitriptyline hydrochloride should be used with caution in patients with impaired liver functions.

Information for Patients: While on therapy with perphenazine and amitriptyline hydrochloride, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with perphenazine and amitriptyline hydrochloride and should counsel them in its appropriate use. A Patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illnesses and Suicidal Thoughts or Actions" is available for perphenazine and amitriptyline hydrochloride. 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 perphenazine and amitriptyline hydrochloride.

Patients should be advised that taking perphenazine 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.

Drug Interactions: ***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.

Perphenazine: Patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, reduced amounts of anesthetics or central nervous system depressants may be necessary.

Since phenothiazines and central nervous system depressants (opiates, analgesics, antihistamines, barbiturates) can potentiate each other, less than the usual dosage of the added drug is recommended and caution is advised when they are administered concomitantly.

Use with caution in patients who are receiving atropine or related drugs because of the additive anticholinergic effects and also in patients who will be exposed to extreme heat or organic phosphate insecticides.

The use of alcohol should be avoided, since additive effects and hypotension may occur. Patients should be cautioned that their response to alcohol may be increased while they are being treated with perphenazine and amitriptyline hydrochloride tablets. The risk of suicide and the danger of overdose may be increased in patients who use alcohol excessively due to the potentiation of the drug's effect.

Amitriptyline Hydrochloride: When amitriptyline hydrochloride is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when amitriptyline is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic type drugs.

This drug may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline hydrochloride and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential.

Discontinue the drug several days before elective surgery, if possible.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) have been associated with elevations in the serum levels of the tricyclic antidepressant when cimetidine is added to the drug regimen. Additionally, higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients taking cimetidine.

Alternatively, decreases in the steady-state serum concentration of the tricyclic antidepressant have been reported in well controlled patients on concurrent therapy upon discontinuance of cimetidine. The therapeutic efficacy of the tricyclic antidepressant may be compromised in these patients as the cimetidine is discontinued.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75 mg to 150 mg of amitriptyline hydrochloride.

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 perphenazine and amitriptyline hydrochloride in a child or adolescent must balance the potential risks with the clinical need.

ADVERSE REACTIONS: To date, clinical evaluation of perphenazine has not revealed any adverse reactions peculiar to the combination. The adverse reactions that occurred were limited to those that have been reported previously for perphenazine and amitriptyline.

Treatment with perphenazine and amitriptyline hydrochloride is commonly associated with sedation, hypertension, neurological impairments and dry mouth.

Perphenazine: The common acute neurological effects of neuroleptic drugs, including perphenazine, consist of dystonia, akathisia or motor restlessness, and pseudoparkinsonism.

More chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the WARNINGS section and below.

The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity.

Neurological: ***Tardive Dyskinesia:*** The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

1. *Dystonia:* Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

2. *Akathisia:* Akathisia presents as constant motor restlessness. The patient with akathisia often complains, **when asked**, about his/her inability to stop moving. Akathisia should **not** be treated with an increased dose of neuroleptic; rather, the dose of antipsychotic may be lowered until the motor restlessness has subsided. The efficacy of anticholinergic treatment of this side effect is unestablished.

3. *Pseudoparkinsonism:* Pseudoparkinsonism refers to a drug-induced state similar to the classic syndrome. Generally, anticholinergic antiparkinsonian agents (i.e., benztropine, biperiden, procyclidine, or trihexphenidyl) and amantadine are helpful in alleviating symptoms that cannot be managed by neuroleptic dose reduction. The value of prophylactic antiparkinsonian drug therapy has not been established. The need for continued use of antiparkinsonian medication should be reevaluated periodically.

Cardiovascular: Hypotension, hypertension, tachycardia, peripheral edema, occasional change in pulse rate, ECG abnormalities (quinidine like effect), reversed epinephrine effect.

CNS and Neuromuscular: Extrapyramidal symptoms, including acute dyskinesia (see Neurological), reactivation of psychoses and production of catatonic like states, paradoxical excitement, ataxia, muscle weakness, hypnotic effects, mild insomnia, lassitude, headache, hyperflexia, altered cerebrospinal fluid proteins.

Autonomic: Urinary frequency or incontinence, dry mouth or salivation, nasal congestion.

Allergic: Anaphylactoid reactions, laryngeal edema, asthma, angioneurotic edema.

Hematologic: Blood dyscrasias including pancytopenia, agranulocytosis, leukopenia, thrombocytopenic purpura, eosinophilia.

Gastrointestinal: Liver damage (jaundice, biliary stasis), obstipation, vomiting, nausea, constipation, anorexia.

Dermatologic: Eczema up to exfoliative dermatitis, urticaria, erythema, itching, photosensitivity.

Ophthalmic: Pigmentation of the cornea and lens, blurred vision.

Endocrine: Lactation, galactorrhea, hyperglycemia, gynecomastia, disturbances in menstrual cycle.

Other: False positive pregnancy tests, including immunologic.

Other adverse reactions that should be considered because they have been reported with various phenothiazine compounds, but not with perphenazine, include:

CNS and Neuromuscular: Grand mal convulsions, cerebral edema.

Gastrointestinal: Polyphagia.

Dermatologic: Photophobia, pigmentation.

Ophthalmic: Pigmentary retinopathy.

Endocrine: Failure of ejaculation.

Amitriptyline Hydrochloride: Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing which follows are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

Cardiovascular: Myocardial infarction, stroke, heart block, arrhythmias, hypotension, particularly orthostatic hypotension, hypertension, tachycardia, palpitation.

CNS and Neuromuscular: Coma, seizures, hallucinations, delusions, confusional states, disorientation, incoordination, ataxia, tremors, peripheral neuropathy, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, dysarthria, disturbed concentration, excitement, anxiety, insomnia, restlessness, nightmares, drowsiness, dizziness, weakness, fatigue, headache, syndrome of inappropriate ADH (antidiuretic hormone) secretion, tinnitus, alteration in EEG patterns.

Anticholinergic: Paralytic ileus, hyperpyrexia, urinary retention, dilatation of urinary tract, constipation, blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis, dry mouth.

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

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

Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice), nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, parotid swelling, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, elevation and lowering of blood sugar levels.

Other: Alopecia, edema, weight gain or loss, urinary frequency, increased perspiration.

Withdrawal Symptoms: After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within 2 weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance. These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants.

OVERDOSAGE*: Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate 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 overdose, therefore, hospital monitoring is required as soon as possible.

Manifestations: Overdosage of perphenazine and amitriptyline hydrochloride tablets may cause any of the adverse reactions listed for perphenazine or amitriptyline hydrochloride.

Overdosage of perphenazine usually produces extrapyramidal symptoms such as dyskinesia and dystonia as described under ADVERSE REACTIONS, but this may be masked by the anticholinergic effects of amitriptyline. Other symptoms may include stupor or coma; children may have convulsive seizures.

Critical manifestations of tricyclic antidepressant overdose includes: 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 alkalinization, to a pH of 7.45 to 7.55, 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 overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION: Since dosage for children has not been established, this product is not recommended for use in children.

The total daily dose of perphenazine and amitriptyline hydrochloride tablets should not exceed 16 mg of perphenazine and 200 mg of amitriptyline hydrochloride.

Initial Dosage: In psychoneurotic patients when anxiety and depression are of such a degree as to warrant combined therapy, one tablet of the 2 mg/25 mg or 4 mg/25 mg three or four times a day or one tablet of the 4 mg/50 mg combination twice a day is recommended.

In more severely ill patients with schizophrenia, the 4 mg/25 mg combination is recommended in an initial dose of two tablets three times a day. If necessary, a fourth dose may be given at bedtime.

In elderly patients and adolescents, and some other patients in whom anxiety tends to predominate, perphenazine and amitriptyline hydrochloride tablet 4 mg/10 mg combination may be administered three or four times a day initially, then adjusted as required for subsequent adequate therapy.

Maintenance Dosage: Depending on the condition being treated, therapeutic response may take from a few days to a few weeks or even longer. After a satisfactory response is noted, dosage should be reduced to the smallest amount necessary to obtain relief from the symptoms for which this product is being administered. A useful maintenance dosage is one tablet of the 2 mg/25 mg or 4 mg/25 mg combination two to four times a day or one tablet of the 4 mg/50 mg combination twice a day. Perphenazine and amitriptyline hydrochloride tablets, 2 mg/10 mg and 4 mg/10 mg can be used to increase flexibility in adjusting maintenance dosage to the lowest amount consistent with relief of symptoms. In some patients, maintenance dosage is required for many months.

HOW SUPPLIED: Perphenazine and Amitriptyline Hydrochloride Tablets, USP are available in the following combinations:

DOSAGE FORM

ACTIVE INGREDIENT	
	2 mg/10 mg
Perphenazine, USP	2
Amitriptyline hydrochloride, USP	10
	2 mg/25 mg
Perphenazine, USP	2
Amitriptyline hydrochloride, USP	25
	4 mg/10 mg
Perphenazine, USP	4
Amitriptyline hydrochloride, USP	10
	4 mg/25 mg
Perphenazine, USP	4
Amitriptyline hydrochloride, USP	25
	4 mg/50 mg
Perphenazine, USP	4
Amitriptyline hydrochloride, USP	50

The 2 mg/10 mg combination tablets are white film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **330** on the other side. They are available as follows:

NDC 0378-0330-01
bottles of 100 tablets
NDC 0378-0330-05
bottles of 500 tablets

The 2 mg/25 mg combination tablets are purple film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **442** on the other side. They are available as follows:

NDC 0378-0442-01
bottles of 100 tablets
NDC 0378-0442-05
bottles of 500 tablets

The 4 mg/10 mg combination tablets are blue film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **727** on the other side. They are available as follows:

NDC 0378-0042-01
bottles of 100 tablets

The 4 mg/25 mg combination tablets are orange film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **574** on the other side. They are available as follows:

NDC 0378-0574-01
bottles of 100 tablets
NDC 0378-0574-05
bottles of 500 tablets

The 4 mg/50 mg combination tablets are purple film-coated, round, unscored tablets debossed with **MYLAN** on one side of the tablet and **73** on the other side. They are available as follows:

NDC 0378-0073-01
bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light.

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.

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

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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, especially 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.

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