

CLOMIPRAMINE HYDROCHLORIDE- clomipramine hydrochloride capsule
Mylan Pharmaceuticals Inc.

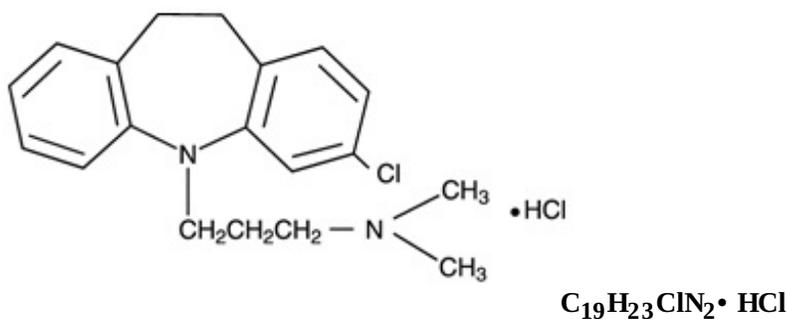
Suicidality and Antidepressant Drugs

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 clomipramine 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. Clomipramine hydrochloride capsules are not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and Pediatric Use.)

DESCRIPTION

Clomipramine hydrochloride is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride, USP is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Clomipramine hydrochloride capsules, USP, for oral administration, contain 25 mg, 50 mg, or 75 mg of clomipramine hydrochloride and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, pregelatinized starch (corn), sodium lauryl sulfate. In addition, the empty gelatin capsules contain: FD&C Red No. 40, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate and titanium dioxide. The following additional product specific coloring agents are employed:

25 mg– FD&C Blue No. 1, D&C Yellow No. 10, and D&C Red No. 28
50 mg– D&C Yellow No. 10 and D&C Red No. 33
75 mg– FD&C Blue No. 1

The imprinting ink contains the following: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, pharmaceutical glaze, propylene glycol and synthetic black iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Pharmacokinetics

Absorption/Bioavailability

Clomipramine from a capsule is as bioavailable as clomipramine from a solution. The bioavailability of clomipramine from capsules is not significantly affected by food.

In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{SS}) and area under plasma concentration time curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25 to 100 mg/day and between 25 to 150 mg/day, although C_{SS} and AUC are approximately linearly related to dose between 100 to 150 mg/day. The relationship between dose and clomipramine/desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{SS} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS: Drug Interactions).

After a single 50 mg oral dose, maximum plasma concentrations of clomipramine occur within 2 to 6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). After multiple daily doses of 150 mg of clomipramine hydrochloride, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. Additional information from a rising dose study of doses up to 250 mg suggests that desmethylclomipramine may exhibit nonlinear pharmacokinetics over the usual dosing range. At a dose of clomipramine hydrochloride 200 mg, subjects who had a single blood sample taken approximately 9 to 22 hours, (median 16 hours), after the dose had plasma concentrations of up to 605 ng/mL for clomipramine, 781 ng/mL for desmethylclomipramine, and 1386 ng/mL for both.

Distribution

Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS: Drug Interactions).

Metabolism

Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD

behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25 mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8% to 1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination

Evidence that the C_{SS} and AUC for clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of clomipramine and desmethylclomipramine are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, clomipramine and desmethylclomipramine may accumulate, and this accumulation may increase the incidence of any dose or plasma concentration dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150 mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7 to 14 days for clomipramine. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for clomipramine is approximately 2.5 and for desmethylclomipramine is 4.6. Importantly, it may take 2 weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of clomipramine have not been determined.

Interactions

Coadministration of haloperidol with clomipramine increases plasma concentrations of clomipramine. Coadministration of clomipramine with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS: Drug Interactions). Younger subjects (18 to 40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of clomipramine were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Clomipramine hydrochloride capsules are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of clomipramine for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10 to 17 years of age. Patients in all studies had moderate to severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive

Compulsive Scale (NIMH-OC). Patients taking clomipramine hydrochloride capsules experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. Clomipramine-treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of clomipramine for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine hydrochloride capsules for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clomipramine hydrochloride capsules are contraindicated in patients with a history of hypersensitivity to clomipramine or other tricyclic antidepressants.

Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with clomipramine or within 14 days of stopping treatment with clomipramine is contraindicated because of an increased risk of serotonin syndrome. The use of clomipramine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).

Starting clomipramine in a patient who is being treated with linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see WARNINGS and DOSAGE AND ADMINISTRATION).

Myocardial Infarction

Clomipramine is contraindicated during the acute recovery period after a 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 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 clomipramine should be written for the smallest quantity of capsules 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 clomipramine is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life threatening serotonin syndrome has been reported with SNRIs and SSRIs, including clomipramine, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of clomipramine with MAOIs intended to treat psychiatric disorders is contraindicated. Clomipramine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking clomipramine. Clomipramine should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

If concomitant use of clomipramine with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with clomipramine and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including clomipramine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Seizures

During premarket evaluation, seizure was identified as the most significant risk of clomipramine hydrochloride use.

The observed cumulative incidence of seizures among patients exposed to clomipramine hydrochloride at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates correct the crude rate of 0.7% (25 of the 3,519 patients) for the variable duration of exposure in clinical trials.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of clomipramine hydrochloride greater

than 250 mg is limited, given that the plasma concentration of clomipramine may be dose dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Caution should be used in administering clomipramine to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Rare reports of fatalities in association with seizures have been reported by foreign post-marketing surveillance, but not in U.S. clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between clomipramine hydrochloride treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide

Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects

Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking clomipramine in clinical trials; but patients were frequently asymptomatic. Among approximately 1,400 patients treated with clomipramine in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion and Other Neuropsychiatric Phenomena

Patients treated with clomipramine have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with clomipramine. As with tricyclic antidepressants to which it is closely related, clomipramine may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania

During premarketing testing of clomipramine in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to clomipramine.

Hepatic Changes

During premarketing testing, clomipramine was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes

Although no instances of severe hematologic toxicity were seen in the premarketing experience with clomipramine, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with clomipramine use. As is the case with tricyclic antidepressants to which clomipramine is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with clomipramine.

Central Nervous System

More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction

The rate of sexual dysfunction in male patients with OCD who were treated with clomipramine in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes

In controlled studies of OCD, weight gain was reported in 18% of patients receiving clomipramine, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving clomipramine had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving clomipramine and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy

As with closely related tricyclic antidepressants, concurrent administration of clomipramine with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery

Prior to elective surgery with general anesthetics, therapy with clomipramine hydrochloride should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use in Concomitant Illness

As with closely related tricyclic antidepressants, clomipramine should be used with caution in the following:

- Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of

cardiac toxicity;

- Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
- Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises;
- Patients with significantly impaired renal function.

Withdrawal Symptoms

A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

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 clomipramine 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 clomipramine. 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 clomipramine.

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.

Physicians are advised to discuss the following issues with patients for whom they prescribe clomipramine hydrochloride:

- The risk of seizure (see WARNINGS);
- The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS: General: Sexual Dysfunction);
- Since clomipramine may impair the mental and/or physical abilities required for the performance of complex tasks, and since clomipramine is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS);
- Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since clomipramine may exaggerate their response to these drugs;

- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
- Patients should notify their physician if they are breast-feeding.

Patients should be advised that taking clomipramine can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Preexisting 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.

Drug Interactions

The risks of using clomipramine in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of clomipramine, caution is advised in using it concomitantly with other CNS active drugs (see PRECAUTIONS: Information for Patients). Clomipramine should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when clomipramine is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with clomipramine because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of clomipramine has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of methylphenidate or hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin), and such an effect may be anticipated with clomipramine as well. Administration of clomipramine has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY: Pharmacokinetics: 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, paroxetine and fluvoxamine, inhibit P450 2D6, they may vary in the extent of inhibition. Fluvoxamine has also been shown to inhibit P450 1A2, an isoform also involved in TCA metabolism. 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 agents in the tricyclic antidepressant class (which includes clomipramine) with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant agent or the other drug. Furthermore, whenever one of these drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant agent may be required. It is desirable to monitor TCA plasma levels whenever an agent of the tricyclic antidepressant class (including clomipramine) is going to be coadministered with another drug known to be an inhibitor of P450 2D6 (and/or P450 1A2).

Because clomipramine is highly bound to serum protein, the administration of clomipramine to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein bound clomipramine by other highly bound drugs (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Distribution).

Monoamine Oxidase Inhibitors (MAOIs)

(See CONTRAINDICATIONS, WARNINGS and DOSAGE AND ADMINISTRATION.)

Serotonergic Drugs

(See CONTRAINDICATIONS, WARNINGS and DOSAGE AND ADMINISTRATION.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found in two 2 year bioassays in rats at doses up to 100 mg/kg, which is 24 and 4 times the maximum recommended human daily dose (MRHD) on a mg/kg and mg/m² basis, respectively, or in a 2 year bioassay in mice at doses up to 80 mg/kg, which is 20 and 1.5 times the MRHD on a mg/kg and mg/m² basis, respectively.

In reproduction studies, no effects on fertility were found in rats given up to 24 mg/kg, which is 6 times, and approximately equal to, the MRHD on a mg/kg and mg/m² basis, respectively.

Pregnancy

Teratogenic Effects

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 100 mg/kg, which is 24 times the maximum recommended human daily dose (MRHD) on a mg/kg basis and 4 times (rats) and 2 times (mice) the MRHD on a mg/m² basis. Slight nonspecific embryo/fetotoxic effects were seen in the offspring of treated rats given 50 and 100 mg/kg and of treated mice given 100 mg/kg.

There are no adequate or well controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken clomipramine hydrochloride until delivery. Clomipramine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clomipramine has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Anyone considering the use of clomipramine in a child or adolescent must balance the potential risks with the

clinical need.

In a controlled clinical trial in children and adolescents (10 to 17 years of age), 46 outpatients received clomipramine for up to 8 weeks. In addition, 150 adolescent patients have received clomipramine in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14 to 17 years of age. The adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that observed in adults.

The risks, if any, that may be associated with clomipramine's extended use in children and adolescents with OCD have not been systematically assessed. The evidence supporting the conclusion that clomipramine is safe for use in children and adolescents is derived from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term clomipramine use on the growth, development, and maturation of children and adolescents. Although there is no evidence to suggest that clomipramine adversely affects growth, development, or maturation, the absence of such findings is not adequate to rule out a potential for such effects in chronic use.

The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of clomipramine in pediatric patients under the age of 10.

Geriatric Use

Clinical studies of clomipramine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects; 152 patients at least 60 years of age participating in various U.S. clinical trials received clomipramine for periods of several months to several years. No unusual age related adverse events were identified in this population. 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

Commonly Observed

The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3,616 patients who received clomipramine in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second most frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

There was no apparent relationship between the adverse events and elevated plasma drug concentrations.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received clomipramine in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving clomipramine (N = 322) or placebo (N = 319) or children treated with clomipramine (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

**Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting Event)**

Body System/ Adverse Event*	<u>Adults</u>		<u>Children and Adolescents</u>	
	Clomipramine hydrochloride (N = 322)	Placebo (N = 319)	Clomipramine hydrochloride (N = 46)	Placebo (N = 44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	-	-
Nervousness	18	2	4	2
Myoclonus	13	-	2	-
Increased appetite	11	2	-	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	-
Twitching	7	1	4	5
Impaired concentration	5	2	-	-
Depression	5	1	-	-
Hypertonia	4	1	2	-
Sleep disorder	4	-	9	5
Psychosomatic disorder	3	-	-	-
Yawning	3	-	-	-
Confusion	3	-	2	-
Speech disorder	3	-	-	-
Abnormal dreaming	3	-	-	2
Agitation	3	-	-	-
Migraine	3	-	-	-
Depersonalization	2	-	2	-
Irritability	2	2	2	-
Emotional lability	2	-	-	2
Panic reaction	1	-	2	-
Aggressive reaction	-	-	2	-

Paresis	-	-	2	-
Skin and Appendages				
Increased sweating	29	3	9	-
Rash	8	1	4	2
Pruritus	6	-	2	2
Dermatitis	2	-	-	2
Acne	2	2	-	5
Dry skin	2	-	-	5
Urticaria	1	-	-	-
Abnormal skin odor	-	-	2	-
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	-	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	-
Flatulence	6	3	-	2
Tooth disorder	5	-	-	-
Gastrointestinal disorder	2	-	-	2
Dysphagia	2	-	-	-
Esophagitis	1	-	-	-
Eructation	-	-	2	2
Ulcerative stomatitis	-	-	2	-
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	-
Flushing	8	-	7	-
Hot flushes	5	-	2	-
Chest pain	4	4	7	-
Fever	4	-	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	-	-
Chills	2	1	-	-
Weight decrease	-	-	7	-
Otitis media	-	-	4	5
Asthenia	-	-	2	-
Halitosis	-	-	2	-
Cardiovascular System				
Postural hypotension	6	-	4	-
Palpitation	4	2	4	-
Tachycardia	4	-	2	-
Syncope	-	-	2	-
Respiratory System				
Pharyngitis	14	9	-	5

Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	-	7	2
Epistaxis	2	-	-	2
Dyspnea	-	-	2	-
Laryngitis	-	1	2	-
Urogenital System				
<i>Male and Female Patients Combined</i>				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	-	-
Micturition frequency	5	3	-	-
Urinary retention	2	-	7	-
Dysuria	2	2	-	-
Cystitis	2	-	-	-
<i>Female Patients Only</i>	(N = 182)	(N = 167)	(N = 10)	(N = 21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	-	-	-
Menstrual disorder	4	2	-	-
Vaginitis	2	-	-	-
Leukorrhea	2	-	-	-
Breast enlargement	2	-	-	-
Breast pain	1	-	-	-
Amenorrhea	1	-	-	-
<i>Male Patients Only</i>	(N = 140)	(N = 152)	(N = 36)	(N = 23)
Ejaculation failure	42	2	6	-
Impotence	20	3	-	-
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	-	4	-
Tinnitus	6	-	4	-
Abnormal lacrimation	3	2	-	-
Mydriasis	2	-	-	-
Conjunctivitis	1	-	-	-
Anisocoria	-	-	2	-
Blepharospasm	-	-	2	-
Ocular allergy	-	-	2	-
Vestibular disorder	-	-	2	2
Musculoskeletal				
Myalgia	13	9	-	-
Back pain	6	6	-	-
Arthralgia	3	5	-	-
Muscle weakness	1	-	2	-
Hemic and Lymphatic				
Purpura	3	-	-	-
Anemia	-	-	2	2
Metabolic and Nutritional				

* Events reported by at least 1% of clomipramine patients are included.

Other Events Observed During the Premarketing Evaluation of Clomipramine

During clinical testing in the U.S., multiple doses of clomipramine were administered to approximately 3,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3,525 individuals exposed to clomipramine who experienced an event of the type cited on at least one occasion while receiving clomipramine. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with clomipramine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole: *Infrequent:* general edema, increased susceptibility to infection, malaise. *Rare:* dependent edema, withdrawal syndrome

Cardiovascular System: *Infrequent:* abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare:* aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia

Digestive System: *Infrequent:* abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare:* cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement

Endocrine System: *Infrequent:* hypothyroidism. *Rare:* goiter, gynecomastia, hyperthyroidism

Hemic and Lymphatic System: *Infrequent:* lymphadenopathy. *Rare:* leukemoid reaction, lymphoma-like disorder, marrow depression

Metabolic and Nutritional Disorder: *Infrequent:* dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare:* fat intolerance, glycosuria

Musculoskeletal System: *Infrequent:* arthrosis. *Rare:* dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis

Nervous System: *Frequent:* abnormal thinking, vertigo. *Infrequent:* abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth grinding. *Rare:* anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide

Respiratory System: *Infrequent:* bronchitis, hyperventilation, increased sputum, pneumonia. *Rare:* cyanosis, hemoptysis, hypoventilation, laryngismus

Skin and Appendages: *Infrequent:* alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare:* chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration

Special Senses: *Infrequent:* abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare:* blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect

Urogenital System: *Infrequent:* endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare:* albuminuria, anorgasmia, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder

Postmarketing Experience

The following adverse drug reaction has been reported during post-approval use of clomipramine. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency.

Eye Disorders: angle-closure glaucoma.

DRUG ABUSE AND DEPENDENCE

Clomipramine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with clomipramine discontinuation (see PRECAUTIONS: General: Withdrawal Symptoms), there is no evidence for drug seeking behavior, except for a single report of potential clomipramine abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received clomipramine hydrochloride for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for clomipramine in foreign marketing, it is not possible to predict the extent to which clomipramine might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

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

Human Experience

In U.S. clinical trials, two deaths occurred in 12 reported cases of acute overdosage with clomipramine either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of clomipramine overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United

Kingdom, clomipramine's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Manifestations

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. 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 toxicity. Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements. Cardiac abnormalities may include tachycardia, signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis, and oliguria or anuria may also be present.

Management

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 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. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a $pCO_2 < 20$ mmHg 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 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.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of clomipramine hydrochloride capsules in 520 adults, and 91 children and adolescents with OCD. During initial titration, clomipramine hydrochloride capsules should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both clomipramine and its active metabolite, desmethylclomipramine, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2 to 3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2 to 3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with clomipramine hydrochloride capsules should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, clomipramine hydrochloride capsules should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS: Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue clomipramine hydrochloride capsules, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of clomipramine after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to one year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with clomipramine hydrochloride capsules. Conversely, at least 14 days should be allowed after stopping clomipramine hydrochloride capsules before starting an MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

Use of Clomipramine Hydrochloride Capsules with Other MAOIs, such as Linezolid or Methylene Blue

Do not start clomipramine hydrochloride capsules in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see CONTRAINDICATIONS).

In some cases, a patient already receiving clomipramine hydrochloride capsules therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, clomipramine hydrochloride capsules should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with clomipramine hydrochloride capsules may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with clomipramine hydrochloride capsules is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS).

HOW SUPPLIED

Clomipramine Hydrochloride Capsules, USP are available containing 25 mg, 50 mg or 75 mg of clomipramine hydrochloride, USP.

The 25 mg capsules are medium orange opaque cap and pink opaque body, hard-shell gelatin capsules filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **3025** in black ink on both the cap and the body. They are available as follows:

NDC 0378-3025-01
bottles of 100 capsules

The 50 mg capsules are yellow opaque cap and pink opaque body, hard-shell gelatin capsules filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **3050** in black ink on both the cap and the body. They are available as follows:

NDC 0378-3050-01
bottles of 100 capsules

The 75 mg capsules are swedish orange opaque cap and pink opaque body, hard-shell gelatin capsules filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **3075** in black ink on both the cap and body. They are available as follows:

NDC 0378-3075-01
bottles of 100 capsules

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

Protect from moisture.

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.

ANIMAL TOXICOLOGY

Phospholipidosis and testicular changes, commonly associated with tricyclic compounds, have been observed with clomipramine. In chronic rat studies, changes related to clomipramine consisted of systemic phospholipidosis, alterations in the testes (atrophy, mineralization) and secondary changes in other tissues. In addition cardiac thrombosis and dermatitis/keratitis were observed in rats treated for 2 years at doses which were 24 and 10 times the maximum recommended human daily dose (MRHD), respectively, on a mg/kg basis, and 4 and 1.5 times the MRHD, respectively, on a mg/m² basis.

MEDICATION GUIDE

CLOMIPRAMINE HYDROCHLORIDE CAPSULES, USP

(kloe mip' ra meen hye'' droe klor' ide)

25 mg, 50 mg and 75 mg

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?

- **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- **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.
- **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:

- | | |
|---|---|
| <ul style="list-style-type: none">• thoughts about suicide or dying• attempts to commit suicide• new or worse depression• new or worse anxiety• feeling very agitated or restless | <ul style="list-style-type: none">• new or worse irritability• acting aggressive, being angry, or violent• acting on dangerous impulses• an extreme increase in activity and talking (mania) |
|---|---|

- panic attacks
- trouble sleeping (insomnia)

- other unusual changes in behavior or mood

Visual problems

- eye pain
- changes in vision
- swelling or redness in or around the eye

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.

Who should not take clomipramine hydrochloride capsules?

Do not take clomipramine hydrochloride capsules if you:

- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 2 weeks of stopping clomipramine hydrochloride capsules unless directed to do so by your physician.
- Do not start clomipramine hydrochloride capsules if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

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.
- **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.

For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

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

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

REVISED AUGUST 2014
CLOM:R19m/MG:CLOM:R2m

PRINCIPAL DISPLAY PANEL - 25 mg

NDC 0378-3025-01

**ClomiPRAMINE
Hydrochloride
Capsules, USP
25 mg**

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**

Rx only 100 Capsules

Each capsule contains:
Clomipramine
hydrochloride, USP 25 mg

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

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

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

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

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

Mylan.com

RM3025A9

	<p>Each capsule contains: Clomipramine hydrochloride, USP 25 mg</p>	<p>NDC 0378-3025-01</p> <p>ClomiPRAMINE Hydrochloride</p> <p>Capsules, USP</p> <p>25 mg</p>  <p>PHARMACIST: Dispense the accompanying Medication Guide to each patient.</p> <p> Mylan®</p> <p>Rx only 100 Capsules</p>	<p>Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep container tightly closed. Keep this and all medication out of the reach of children. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from moisture. Usual Dosage: See accompanying prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A.</p> <p> Mylan® Mylan.com</p> <p>RM3025A9</p>
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PRINCIPAL DISPLAY PANEL - 50 mg

NDC 0378-3050-01

**ClomiPRAMINE
Hydrochloride
Capsules, USP
50 mg**

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**

Rx only 100 Capsules

Each capsule contains:
Clomipramine
hydrochloride, USP 50 mg

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

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

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

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

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

Mylan.com

RM3050A9

NDC 0378-3050-01

**ClomiPRAMINE
Hydrochloride**

Capsules, USP

50 mg

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**

Mylan®

Rx only 100 Capsules

Each capsule contains:
Clomipramine
hydrochloride, USP 50 mg

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

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

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

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

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

Mylan®
Mylan.com

RM3050A9

PRINCIPAL DISPLAY PANEL - 75 mg

NDC 0378-3075-01

**ClomiPRAMINE
Hydrochloride
Capsules, USP
75 mg**

**PHARMACIST: Dispense the accompanying
Medication Guide to each patient.**

Rx only 100 Capsules

Each capsule contains:
Clomipramine
hydrochloride, USP 75 mg

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

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

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

Protect from moisture.

Usual Dosage: See accompanying
prescribing information.

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

Mylan.com

RM3075A9

	<p>Each capsule contains: Clomipramine hydrochloride, USP 75 mg</p>	<p>NDC 0378-3075-01</p> <p>ClomiPRAMINE Hydrochloride</p> <p>Capsules, USP</p> <p>75 mg</p>  <p>PHARMACIST: Dispense the accompanying Medication Guide to each patient.</p> <p> Mylan®</p> <p>Rx only 100 Capsules</p>	<p>Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.</p> <p>Keep container tightly closed.</p> <p>Keep this and all medication out of the reach of children.</p> <p>Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]</p> <p>Protect from moisture.</p> <p>Usual Dosage: See accompanying prescribing information.</p> <p>Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A.</p> <p> Mylan® Mylan.com</p> <p>RM3075A9</p>
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CLOMIPRAMINE HYDROCHLORIDE

clomipramine hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3025
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	25 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6B30)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: HBR47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	ORANGE (medium orange opaque) , PINK (light pink opaque)	Score	no score
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	MYLAN;3025
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3025-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/11/1998	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074947	05/11/1998	

CLOMIPRAMINE HYDROCHLORIDE

clomipramine hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3050
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	50 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
D&C RED NO. 33 (UNII: 9DBA0SBB0L)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	YELLOW (yellow opaque) , PINK (light pink opaque)	Score	no score
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	MYLAN;3050
Contains			

Packaging

		Marketing Start	Marketing End
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3050-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/11/1998	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074947	05/11/1998	

CLOMIPRAMINE HYDROCHLORIDE			
clomipramine hydrochloride capsule			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0378-3075
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
	Ingredient Name	Basis of Strength	Strength
	CLOMIPRAMINE HYDROCHLORIDE (UNII: 2LXW0L6GWJ) (CLOMIPRAMINE - UNII:NUV44L116D)	CLOMIPRAMINE HYDROCHLORIDE	75 mg
Inactive Ingredients			
	Ingredient Name	Strength	
	STARCH, CORN (UNII: O8232NY3SJ)		
	GELATIN (UNII: 2G86QN327L)		
	MAGNESIUM STEARATE (UNII: 70097M6B30)		
	PROPYLENE GLYCOL (UNII: 6DC9Q167V3)		
	FERRIC OXIDE RED (UNII: 1K09F3G675)		
	SILICON DIOXIDE (UNII: ETJ7Z6XBU4)		
	SODIUM LAURYL SULFATE (UNII: 368GB5141J)		
	FERROSFERRIC OXIDE (UNII: XM0M87F357)		
	TITANIUM DIOXIDE (UNII: 15FIX9V2JP)		
	FD&C RED NO. 40 (UNII: WZB9127XOA)		
	D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)		
	FD&C BLUE NO. 1 (UNII: HBR47K3TBD)		
	FD&C BLUE NO. 2 (UNII: L06K8R7DQK)		
	SHELLAC (UNII: 46N107B71O)		
Product Characteristics			
Color	ORANGE (swedish orange opaque) , PINK (light pink opaque)	Score	no score
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	MYLAN;3075
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3075-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/11/1998	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074947	05/11/1998	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

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Mylan Pharmaceuticals Inc.