Anafranil[®] Clomipramine Hydrochloride Capsules USP (25 mg, 50 mg, and 75 mg)

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of clomipramine hydrochloride or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. Anafranil is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Anafranil[®], (clomipramine hydrochloride capsules USP), is an antiobsessional drug that belongs to the class (diben zazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

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

$$\begin{array}{c} \text{CI} \\ \text{CH}_2\text{CH}_2\text{CH}_2\text{-N}, \text{CH}_3 \\ \text{CH}_3 \end{array} \text{.} \text{HCI} \\ \text{C}_{19}\text{H}_{23}\text{CIN}_2\text{°} \text{HCI} \\ \text{MW} = 351.31 \end{array}$$

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.

Inactive Ingredients. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch (corn), and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{SS}) and areain a duse projointoning study involving intuitiple twin obess, steady-state plasma-concentrations (tags, 3 and atea—under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desemblyIclomipramine (DMI), 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 Css, and AUC are approximately linearly related to dose between 100 to 150 mg/day. The relationship between dose and CMI/DMI 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 Css 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). Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI 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 Anafranil, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for CMI and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for DMI. Additional information from a rising dose study of doses up to 250 mg suggests that DMI may exhibit nonlinear pharmacokinetics over the usual dosing range. At a dose of Anafranii 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 CMI, 781 ng/mL for DMI, and 1386 ng/mL for both.

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

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI 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 CMI 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 CMI and DMI were only about 0.8% to 1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

mates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI 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, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasmaconcentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI 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 CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been

Interactions: Co-administration of haloperidol with CMI increases plasma concentrations of CMI. Co-administration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18 to 40 years of age) tolerated CMI 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 CMI were significantly lower in smokers than in nonsmokers.

INDICATIONS AND USAGE

Anafranii is 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 Anafranil 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 CMI 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. CMItreated 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 Anafranil 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 Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Anafranil® (clomipramine hydrochloride capsules USP) is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants

Anafranii should not be given in combination, or within 14 days before or after treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations. Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

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. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would genreally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, 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 nonpsy-chiatric. 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 pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for clomipramine hydrochloride should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

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 hydrochloride is not approved for use in treating bipolar depression

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

The observed cumulative incidence of seizures among patients exposed to Anafranil 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 3519 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 CMI greater than 250 mg is limited, given that the plasma concentration of CMI 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 Anafranil 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, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions. Thus a causal association between Anafranil treatment and these fatalities has not been established.

Physicians should discuss with patients the risk of taking Anafranil 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

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil 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 Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had EC6s, 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 EC6 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 Anafranil 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 Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia

Mania/Hypomania: During premarketing testing of Anafranil 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 Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGP (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 postmarketing 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 Anafranil, there have been postmarketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil® (clomipramine hydrochloride capsules USP) use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic postmarketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs. When Anafranil and a neu-roleptic 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 Anafranil in the pre-Sexual Dystriction. The late of sexual dystriction in that patients with OSB with Most exceeding the American and a marketing experience with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% 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 Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil 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 Anafranil 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 Anafranil 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 Anafranil 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, Anafranil should be used with caution in the

- (1) Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity;
- (2) Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug;
- (3) Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke
- (4) Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, 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 Anafranil 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).

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with clomipramine hydrochloride and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for clomipramine 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 clomipramine hydrochloride.

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, nostility, 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 observe 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 iated 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 Anafranil:

- (1) The risk of seizure (see WARNINGS);
- (2) The relatively high incidence of sexual dysfunction among males (see Sexual Dysfunction);
- (3) Since Anafranil may impair the mental and/or physical abilities required for the performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS):
- (4) Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs;
- (5) Patients should notify their physician if they become pregnant or intend to become pregnant during therapy;
- (6) Patients should notify their physician if they are breast-feeding.

Drug Interactions

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

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs. Several tricyclic antidepressants have been reported to block the pharmacologic effects of quanethidine, clonidine

or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI 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 CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, 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 anti-depressants (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, suf-ficient 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 antide-pressant class (which includes Anafranil) 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 co-therapy, 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 Anafranil is going to be co-administered with another drug known to be an inhibitor of P450 2D6 (and/or P450 1A2).

Because Anafranil is highly bound to serum protein, the administration of Anafranil 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 Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

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/m^2 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/m^2 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 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/m² 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 Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers

Anafranii[®] (clomipramine hydrochloride capsules USP) 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.

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 Anafranil 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 Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranii 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 Anafranil's extended use in children and adolescents with OCD have not been systematically assessed. The evidence supporting the conclusion that Anafranil 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 Anafranil use on the growth. development, and maturation of children and adolescents. Although there is no evidence to suggest that Anafranii 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 Anafranil in pediatric patients under the age of 10

Geriatric Use

Clinical studies of Anafranil 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 Anafranil 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 Anafranil 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 3616 patients who received Anafranil 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 com plaints, 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 Anafranii in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranii (N=322) or placebo (N=319) or children treated with Anafranii (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

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

	Adults		Children and Adolescents	
Body System/ Adverse Event*	Anafranil (N=322)	Placebo (N=319)	Anafranil (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	-	-

Anafranil®

Clomipramine H	yurocinoriue	capsules our	
Depression	5	1	-
Hypertonia	4 4	1	2
Sleep disorder Psychosomatic disorder	3	-	9
Yawning	3	-	-
Confusion	3	_	2
Speech disorder	3	-	-
Abnormal dreaming	3	-	-
Agitation	3	-	-
Migraine	3	-	-
Depersonalization	2	-	2
Irritability	2	2	2
Emotional lability	2	-	2
Panic reaction Aggressive reaction	1	-	
Aggressive reaction Paresis	-	-	2 2
Skin and Appendages ncreased sweating	29	3	9
Rash	8	1	4
Pruritus	6		2
Dermatitis	2	-	-
Acne	2	2	-
Dry skin	2	-	-
Jrticaria	1	-	-
Abnormal skin odor	-	-	2
Digestive System			
Dry mouth	84	17	63
Constipation	47	11	22
Nausea	33	14	9
Dyspepsia	22	10	13
Diarrhea	13	9	7
Anorexia	12	-	22
Abdominal pain	11	9	13
/omiting	7	2	7
latulence	6	3	-
Tooth disorder	5	-	-
Gastrointestinal disorder	2	-	-
Dysphagia	2	-	-
Esophagitis Eructation	1	-	2
ructation Jicerative stomatitis	-	-	2
	_	-	4
Body as a Whole			
Fatigue	39	18	35
Weight increase	18 8	1	2 7
Flushing Hot flushes	5	-	2
Chest pain	4	4	7
Fever	4	-	2
Allergy	3	3	7
Pain	3	2	4
Local edema	2	4	-
Chills	2	1	-
Weight decrease	-	-	7
Otitis media	-	-	4
Asthenia Halitosis	-	-	2 2
idiitosis			۷
Cardiovascular System			
Postural hypotension	6	-	4
Palpitation	4 4	2	4
Tachycardia Syncope	4 -	-	2 2
			-
Respiratory System	1.4	0	
Pharyngitis Rhinitis	14 12	9 10	7
Sinusitis	6	4	2
Coughing	6	6	4
Bronchospasm	2	-	7
Epistaxis	2	-	-
Dyspnea	-	Ī	2
aryngitis	-	1	2
Jrogenital System			
Male and Female Patients		÷	
Micturition disorder	14	2	4
Jrinary tract infection	6 5	1 3	-
Micturition frequency Jrinary retention	5 2	3 -	7
Dysuria	2	2	-
Cystitis	2	-	-
Female Patients Only	(N=182)	(N=167)	(N=10)
Dysmenorrhea	12	` 14	10
actation (nonpuerperal)	4	-	-
Menstrual disorder	4	2	-
/aginitis	2	-	-
_eukorrhea	2	-	-
Breast enlargement Breast pain	2 1	-	-
	1	-	-
	(N=140)	(N=152)	(N=36)
Amenorrhea	\	2	6
Amenorrhea Male Patients Only	42		
Amenorrhea Male Patients Only Ejaculation failure	42 20	3	-
Amenorrhea Male Patients Only Ejaculation failure mpotence		3	-
Amenorrhea Male Patients Only Ejaculation failure mpotence Special Senses		3	7
Amenorrhea Male Patients Only Ejaculation failure mpotence Special Senses Abnormal vision	20 18		
Amenorrhea Male Patients Only Ejaculation failure mpotence Special Senses Abnormal vision Taste perversion	20	4	7
Amenorrhea Male Patients Only Ejaculation failure Impotence Special Senses Abnormal vision Taste perversion Tinnitus	20 18 8	4	7 4
Amenorrhea Male Patients Only jaculation failure mpotence Special Senses Abnormal vision faste perversion Tinnitus Abnormal lacrimation	20 18 8 6 3 2	4 - 2	7 4 4 -
Amenorrhea Male Patients Only Ejaculation failure Impotence Special Senses Abnormal vision Taste perversion Tinnitus Abnormal lacrimation Mydriasis Conjunctivitis	20 18 8 6 3	4	7 4 4 -
Amenorrhea Male Patients Only jaculation failure Impotence Special Senses Abnormal vision Taste perversion Tinnitus Abnormal lacrimation Mydriasis Conjunctivitis Anisocoria	20 18 8 6 3 2 1	4 2	7 4 4 - - - 2
Amenorrhea Male Patients Only Ejaculation tailure Impotence Special Senses Abnormal vision Taste perversion Tinnitus Abnormal lacrimation Mydriasis Conjunctivitis Aniocoria Blepharospasm	20 18 8 6 3 2 1	4	7 4 4 - - 2 2
Amenorrhea Male Patients Only jaculation failure Impotence Special Senses Abnormal vision Taste perversion Tinnitus Abnormal lacrimation Mydriasis Conjunctivitis Anisocoria	20 18 8 6 3 2 1	4 2	7 4 4 - - - 2

Musculoskeletal Myalgia Back pain Arthralgia	13 6 3	9 6 5	- -	- - -
Muscle weakness	1	-	2	-
Hemic and Lymphatic Purpura Anemia	3 -	-	2	2
Metabolic and Nutritional Thirst	2	2	-	2

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

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil® (clomipramine hydrochloride capsules USP) were administered to approximately 3600 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 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. 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 Anafranii, 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 1/1000 patients; rare events are those occurring in less than 1/1000

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, Bare 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. gas troesophageal 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, Bare - leukemoid reaction, lymphoma-like disorder mar-

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, suicidal attempt, teeth-grinding. Rare - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome. choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hypereflexia, hypoesthesia, illusion, impaired impulse control, indeci-siveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor,

Respiratory System: Infrequent - bronchitis, hyperventilation, increased sputum, pneumonia. Rare - cyanosis, hemoptysis, hypoventilation, larvngismus,

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, *Bare* - 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, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranii 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 Anafranii discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil 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.

(N=21)

(N=23)

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, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil 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 Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon postmarketing reports in the United Kingdom, CMI'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, and 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.

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 dysrbythmias 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 ORS 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 Pco₂ < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or pheny toin. 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 overdosages 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 Anafranil in 520 adults, and 91 children and adolescents with OCD, During initial titration, Anafranil 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 CMI and its active metabolite, DMI, 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

Initial Treatment/Dose Adjustment (Adults)
Treatment with Anafranil 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, Anafranil 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

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 Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 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.

Anafranil® (clomipramine hydrochloride capsules USP) Capsules 25 mg - ivory/melon yellow (imprinted ANAFRANIL 25 mg)

Bottles of 100	NDC 0406-9906-01
Capsules 50 mg - ivory/aqua blue (imprinted ANAFRANIL 50 mg) Bottles of 100	NDC 0406-9907-01

Capsules 75 mg - ivory/yellow (imprinted ANAFRANIL 75 mg) . .NDC 0406-9908-01 Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Dispense in well-closed containers with a child-resistant closure. Protect from moisture

ANIMAL TOXICOLOGY

Phospholipidosis and testicular changes, commonly associated with tricyclic compounds, have been observed with Anafranil. In chronic rat studies, changes related to Anafranil consisted of systemic phospholipidosis, alterations in the testes (atrophy, mineralization) and secondary changes in other tissues. In addition cardiac thrombosis and dermatitis/ke atitis 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.

Anafranil is a registered trademark of Mallinckrodt Inc.

Manufactured by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936 for Mallinckrodt Inc. St. Louis, M0 63134 U.S.A.



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Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

- 1. There is a risk of suicidal thoughts or actions
- 2. How to try to prevent suicidal thoughts or actions in your child
- 3. You should watch for certain signs if your child is taking an antidepressant
- 4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill vourself is called suicidality or being suicidal.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. *No one committed suicide in these studies*, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- · A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

- After starting an antidepressant, your child should generally see his or her healthcare provider:
- . Once a week for the first 4 weeks
- · Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back More often if problems or questions arise (see Section 3)
- You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider right away if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- · Attempts to commit suicide • New or worse depression
- New or worse anxiety
- · Feeling very agitated or restless
- Panic attacks • Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptom

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac™) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac™), sertraline (Zoloft™), fluvoxamine, and clomipramine (Anafranil™)

Your healthcare provider may suggest other antidepressants based on the past experience of vour child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

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*Zoloft® is a registered trademark of Pfizer Pharmaceutical

*Anafranil® is a registered trademark of Mallinckrodt Inc.

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

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