

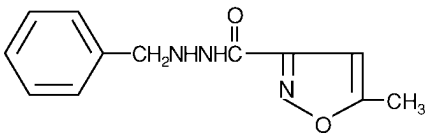
**TABLETS**

**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 Marplan 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. Marplan is not approved for use in pediatric patients. (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:** Marplan (isocarboxazid), a monoamine oxidase inhibitor, is available for oral administration in 10-mg tablets. Each tablet also contains lactose, corn starch, povidone, D&C Red No. 27, FD&C Yellow No. 3, and magnesium stearate. Chemically, isocarboxazid is 5-methyl-3-isoxazolecarboxylic acid 2-benzylhydrazide. The structural formula is:



Isocarboxazid is a colorless, crystalline substance with very little taste.

**CLINICAL PHARMACOLOGY: Pharmacodynamics:** Isocarboxazid is a non-selective hydrazine monoamine oxidase (MAO) inhibitor. In vivo and in vitro studies demonstrated inhibition of MAO in the brain, heart, and liver. The mechanism by which MAO inhibitors act as antidepressants is not fully understood, but it is thought to involve the elevation of brain levels of biogenic amines. However, MAO is a complex enzyme system, widely distributed throughout the body, and drugs that inhibit MAO in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition per se, other pharmacologic actions, or an interaction of both is responsible for the antidepressant effects observed.

**Pharmacokinetics:** Marplan pharmacokinetic information is not available.

**Clinical Efficacy Data:** The effectiveness of Marplan was demonstrated in two 6-week placebo-controlled studies conducted in adult outpatients with depressive symptoms that corresponded to the DSM-IV category of major depressive disorder. The patients often also had signs and symptoms of anxiety (anxious mood, panic, and/or phobic symptoms). Patients were initiated with a dose of 10 mg bid, with increases every 2 to 4 days, as tolerated, until a therapeutic effect was achieved, up to a maximum dose of 80 mg/day. Doses were administered on a divided schedule ranging from 2 to 4 times a day. The mean dose overall for both studies was approximately 40 mg/day, with very few patients receiving doses greater than 60 mg/day. In both studies at the end of 6 weeks, patients receiving Marplan had significantly greater reduction in signs and symptoms of depression evaluated by the Hamilton Depression Scale, for both the Total Score and the Depressed Mood Score, than patients who received placebo.

**INDICATIONS AND USAGE:** Marplan is indicated for the treatment of depression. Because of its potentially serious side effects, Marplan is not an antidepressant of first choice in the treatment of newly diagnosed depressed patients.

The efficacy of Marplan in the treatment of depression was established in 6-week controlled trials of depressed outpatients. These patients had symptoms that corresponded to the DSM-IV category of major depressive disorder; however, they often also had signs and symptoms of anxiety (anxious mood, panic, and/or phobic symptoms) (See CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant effectiveness of Marplan in hospitalized depressed patients, or in endogenomorphically retarded and delusionally depressed patients, has not been adequately studied.

The effectiveness of Marplan in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Marplan for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

**CONTRAINDICATIONS:** Marplan (isocarboxazid) should not be administered in combination with any of the following: MAO inhibitors or dibenzazepine derivatives; sympathomimetics (including amphetamines); some central nervous system depressants (including narcotics and alcohol); antihypertensive, diuretic, antihistaminic, sedative or anesthetic drugs, bupropion HCL, buspirone HCL, dextromethorphan, cheese or other foods with a high tyramine content; or excessive quantities of caffeine.

Marplan (isocarboxazid) should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease, hypertension, or history of headache.

**Contraindicated Patient Populations: Hypersensitivity:** Marplan should not be used in patients with known hypersensitivity to isocarboxazid.

**Cerebrovascular Disorders:** Marplan should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease or hypertension.

**Pheochromocytoma:** Marplan should not be used in the presence of pheochromocytoma, as such tumors secrete pressor substances whose metabolism may be inhibited by Marplan.

**Liver Disease:** Marplan should not be used in patients with a history of liver disease, or in those with abnormal liver function tests.

**Renal Impairment:** Marplan should not be used in patients with severe impairment of renal function.

**Contraindicated MAOI-Other Drug Combinations: Other MAOI Inhibitors or With Dibenzazepine-Related Entities:** Marplan should not be administered together with, or in close proximity to, other MAO inhibitors or dibenzazepine-related entities. Hypertensive crises, severe convulsive seizures, coma, or circulatory collapse may occur in patients receiving such combinations.

In patients being transferred to Marplan from another MAO inhibitor or from a dibenzazepine-related entity, a medication-free interval of at least 1 week should be allowed, after which Marplan therapy should be started using half the normal starting dosage for at least the first week of therapy. Similarly, at least 1 week should elapse between the discontinuation of Marplan and initiation of another MAO inhibitor or dibenzazepine-related entity, or the readministration of Marplan. The following list includes some other MAO inhibitors, dibenzazepine-related entities, and tricyclic antidepressants.

Generic Name	Trademark (Manufacturer)
<b>Other MAO Inhibitors</b>	
Furazolidone	Furoxone® (Roberts Laboratories)
Pargyline HCL	Eutonyl® (Abbott Laboratories)
Pargyline HCL and methylothiazide	Eutron® (Abbott Laboratories)
Phenelzine sulfate	Nardil® (Parke-Davis)
Procabazine	Matulane® (Roche Laboratories)
Tranlycypromine sulfate	Parnate® (SmithKline Beecham Pharmaceuticals)
<b>Dibenzazepine-Related and Other Tricyclics</b>	
Amitriptyline HCL	Elavil® (Zeneca)

## MARPLAN® (isocarboxazid)

Generic Name	Trademark (Manufacturer)
Perphenazine and amitriptyline HCL	Endep® (Roche Products) Etrafon® (Schering) Triavil® (Merck Sharp & Dohme)
Clomipramine hydrochloride	Anafranil® (Novartis)
Desipramine HCL	Norpramin® (Hoechst Marion Roussel) Pertofrane® (Rhône-Poulenc Rorer Pharmaceuticals) Janimine® (Abbott Laboratories)
Imipramine HCL	Tofranil® (Novartis)
Nortriptyline HCL	Aventyl® (Eli Lilly & Co.) Pamelor® (Novartis)
Protriptyline HCL	Vivactil® (Merck Sharp & Dohme)
Doxepin HCL	Adapin® (Fisons) Sinequan® (Pfizer)
Carbamazepine	Tegretol® (Novartis)
Cyclobenzaprine HCL	Flexeril® (Merck Sharp & Dohme)
Amoxapine	Asendin® (Lederle)
Maprotiline HCL	Ludimil® (Novartis)
Trimipramine maleate	Surmontil® (Wyeth-Ayerst Laboratories)

**Bupropion:** The concurrent administration of a MAO inhibitor and bupropion hydrochloride (Wellbutrin®, and Zyan®, Glaxo Wellcome) is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride.

**Selective Serotonin Reuptake Inhibitors (SSRIs):** Marplan should not be administered in combination with any SSRI. There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation and confusion progressing to delirium and coma) in patients receiving fluoxetine (Prozac®, Lilly) in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Fluoxetine and other SSRIs should therefore not be used in combination with Marplan, or within 14 days of discontinuing therapy with Marplan. As fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine before starting Marplan. At least 2 weeks should be allowed after stopping sertraline (Zoloft®, Pfizer) or paroxetine (Paxil®, SmithKline Beecham Pharmaceuticals) before starting Marplan. In addition, there should be an interval of at least 10 days between discontinuation of Marplan and initiation of fluoxetine or other SSRIs.

**Buspiprone:** Marplan should not be used in combination with buspiprone HCL (Buspar®, Bristol Myers Squibb); several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspiprone HCL. At least 10 days should elapse between the discontinuation of Marplan and the institution of buspiprone HCL. Serious reactions may also occur when MAO inhibitors are given with serotonergic drugs (e.g., dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxine).

**Sympathomimetics:** Marplan should not be administered in combination with sympathomimetics, including amphetamines, or with over-the-counter drugs such as cold, hay fever, or weight-reducing preparations that contain vasoconstrictors.

During Marplan therapy, it appears that some patients are particularly vulnerable to the effects of sympathomimetics when the activity of metabolizing enzymes is inhibited. Use of sympathomimetics and compounds such as guanethidine, methyl dopa, methylphenidate, reserpine, epinephrine, norepinephrine, phenylalanine, dopamine, levodopa, tyrosine, and tryptophan with Marplan may precipitate hypertension, headache, and related symptoms. The combination of MAO inhibitors and tryptophan has been reported to cause behavioral and neurologic symptoms, including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations, and Babinski signs.

**Meperidine:** Meperidine should not be used concomitantly with MAO inhibitors or within 2 or 3 weeks following MAO therapy. Serious reactions have been precipitated with concomitant use, including coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse, and death. It is thought that these reactions may be mediated by accumulation of 5-HT (serotonin) consequent to MAO inhibition.

**Dextromethorphan:** Marplan should not be used in combination with dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior.

**Cheese or Other Foods With a High Tyramine Content:** Hypertensive crises have sometimes occurred during Marplan therapy after ingestion of foods with a high tyramine content. In general, patients should avoid protein foods in which aging or protein breakdown is used to increase flavor. In particular, patients should be instructed not to take foods such as cheese (particularly strong or aged varieties), sour cream, Chianti wine, sherry, beer (including non-alcoholic beer), liqueurs, pickled herring, anchovies, caviar, liver, canned figs, raisins, bananas or avocados (particularly if overripe), chocolate, soy sauce, sauerkraut, the pods of broad beans (fava beans), yeast extracts, yogurt, meat extracts, meat prepared with tenderizers, or dry sausage.

**Anesthetic Agents:** Patients taking Marplan should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of Marplan and spinal anesthesia should be kept in mind. Marplan should be discontinued at least 10 days before elective surgery.

**CNS Depressants:** Marplan should not be used in combination with some central nervous system depressants, such as narcotics, barbiturates, or alcohol.

**Antihypertensives:** Marplan should not be used in combination with antihypertensive agents, including thiazide diuretics. A marked potentiating effect on these drugs has been reported, resulting in hypotension.

**Caffeine:** Excessive use of caffeine in any form should be avoided in patients receiving Marplan.

### WARNINGS TO PHYSICIANS:

#### 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 nine 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 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 generally 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**

## MARPLAN<sup>®</sup> (isocarboxazid)

**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 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 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 Marplan 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 these 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 Marplan is not approved for use in treating bipolar depression.

**WARNINGS: Second Line Status:** Marplan can cause serious side effects. It is not recommended as initial therapy but should be reserved for patients who have not responded satisfactorily to other antidepressants.

**Hypertensive Crises: The most important reaction associated with MAO inhibitors is the occurrence of hypertensive crises, which have sometimes been fatal, resulting from the co-administration of MAOIs and certain drugs and foods (see CONTRAINDICATIONS).**

These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea or vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), and photophobia. Either tachycardia or bradycardia may be present, and associated constricting chest pain and dilated pupils may occur. Intracranial bleeding, sometimes fatal, has been reported in association with the increase in blood pressure.

Blood pressure should be followed closely in patients taking Marplan to detect any pressor response.

Therapy should be discontinued immediately if palpitations or frequent headaches occur during Marplan therapy as these symptoms may be prodromal of a hypertensive crisis.

If a hypertensive crisis occurs, Marplan should be discontinued, and therapy to lower blood pressure should be instituted immediately. Although there has been no systematic study of treatment of hypertensive crisis, phentolamine (available as Regitine®, Novartis) has been used and is recommended at a dosage of 5 mg IV. Care should be taken to administer the drug slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling. Other symptomatic and supportive measures may be desirable in particular cases. Parenteral reserpine should not be used.

**Warnings to the Patient:** Patients should be instructed to report promptly the occurrence of headache or other unusual symptoms, i.e., palpitation and/or tachycardia, a sense of constriction in the throat or chest, sweating, dizziness, neck stiffness, nausea, or vomiting. Patients should be warned against eating the foods listed under CONTRAINDICATIONS while on Marplan therapy and should also be

told not to drink alcoholic beverages. The patient should also be warned about the possibility of hypotension and faintness, as well as drowsiness sufficient to impair performance of potentially hazardous tasks, such as driving a car or operating machinery.

Patients should also be cautioned not to take concomitant medications, whether prescription or over-the-counter drugs such as cold, hay fever, or weight-reducing preparations, without the advice of a physician. They should be advised not to consume excessive amounts of caffeine in any form. Likewise, they should inform their physicians and their dentist about the use of Marplan.

**Limited Experience With Marplan at Higher Doses:** Because of the limited experience with systematically monitored patients receiving Marplan at the higher end of the currently recommended dose range of up to 60 mg/day, caution is indicated in patients for whom a dose of 40 mg/day is exceeded (see ADVERSE REACTIONS).

### PRECAUTIONS:

#### 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 Marplan and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Marplan. 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 Marplan.

**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 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 associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

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

Anyone considering the use of Marplan in a child or adolescent must balance the potential risks with the clinical need.

**General: Hypotension:** Hypotension has been observed during Marplan therapy. Symptoms of postural hypotension are seen most commonly, but not exclusively, in patients with preexistent hypertension; blood pressure usually returns rapidly to pretreatment levels upon discontinuation of the drug. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the beginning of therapy. Postural hypotension may be relieved by having the patient lie down until blood pressure returns to normal. When Marplan is combined with phenothiazine derivatives or other compounds known to cause hypotension, the possibility of additive hypotensive effects should be considered.

**Lower Seizure Threshold:** Because Marplan lowers the convulsive threshold in some animal experiments, suitable precautions should be taken if epileptic patients are treated. Marplan appears to have varying effects in epileptic patients; while some have a decrease in frequency of seizures, other have more seizures.

Drugs that lower the seizure threshold, including MAO inhibitors, should not be used with Amipaque® (metrizamide, Sanofi Winthrop Pharmaceuticals). As with other MAO inhibitors, Marplan should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.

**Hepatotoxicity:** There is a low incidence of altered liver function or jaundice in patients treated with Marplan. In the past, it was difficult to differentiate most cases of drug-induced hepatocellular jaundice from viral hepatitis although this is no longer true. Periodic liver chemistry tests should be performed during Marplan therapy; use of the drug should be discontinued at the first sign of hepatic dysfunction or jaundice.

## MARPLAN<sup>®</sup> (isocarboxazid)

**Suicide:** In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety or agitation. Also, some patients fail to respond to drug therapy or may respond only temporarily. The strictest supervision, and preferably hospitalization, are required.

**Use in Patients With Concomitant Illness:** MAO inhibitors can suppress anginal pain that would otherwise serve as a warning of myocardial ischemia.

In patients with impaired renal function, Marplan should be used cautiously to prevent accumulation.

Some MAO inhibitors have contributed to hypoglycemic episodes in diabetic patients receiving insulin or glyceamic agents. Marplan should therefore be used with caution in diabetics using these drugs.

Marplan may aggravate coexisting symptoms in depression, such as anxiety and agitation.

Use Marplan with caution in hyperthyroid patients because of their increased sensitivity to pressor amines.

Marplan should be used cautiously in hyperactive or agitated patients, as well as in schizophrenic patients, because it may cause excessive stimulation. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with marketed antidepressants.

**Drug Interactions:** See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections for information on drug interactions.

Marplan should be administered with caution to patients receiving Antabuse<sup>®</sup> (disulfiram, Wyeth-Ayerst Laboratories). In a single study, rats given high intraperitoneal doses of an MAO inhibitor plus disulfiram experienced severe toxicity, including convulsions and death.

Concomitant use of Marplan and other psychotropic agents is generally not recommended because of possible potentiating effects. This is especially true in patients who may subject themselves to an overdosage of drugs. If combination therapy is needed, careful consideration should be given to the pharmacology of all agents to be used. The monoamine oxidase inhibitory effects of Marplan may persist for a substantial period after discontinuation of the drug, and this should be borne in mind when another drug is prescribed following Marplan. To avoid potentiation, the physician wishing to terminate treatment with Marplan and begin therapy with another agent should allow for an interval of 10 days.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies to evaluate carcinogenic potential have not been conducted with this drug, and there is no information concerning mutagenesis or impairment of fertility.

**Pregnancy Category C:** The potential reproductive toxicity of isocarboxazid has not been adequately evaluated in animals. It is also not known whether isocarboxazid can cause embryo/fetal harm when administered to a pregnant woman or can affect reproductive capacity. Marplan should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** Levels of excretion of isocarboxazid and/or its metabolites in human milk have not been determined, and effects on the nursing infant are unknown. Marplan should be used in women who are nursing only if clearly needed.

**Pediatric Use:** Marplan is not recommended for use in patients under 16 years of age, as safety and effectiveness in pediatric populations have not been demonstrated.

**ADVERSE REACTIONS: Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:** Systematically collected data are available from only 86 patients exposed to Marplan, of whom only 52 received doses of  $\geq 50$  mg/day, including only 11 who were dosed at  $\geq 60$  mg/day. Because of the limited experience with systematically monitored patients receiving Marplan at the higher end of the currently recommended dose range of up to 60 mg/day, caution is indicated in patients for whom a dose of 40 mg/day is exceeded (see WARNINGS).

The table that follows enumerates the incidence, rounded to the nearest percent, of treatment emergent adverse events that occurred among 86 depressed patients who received Marplan at doses ranging from 20 to 80 mg/day in placebo-controlled trials of 6 weeks in duration. Events included are those occurring in 1% or more of patients treated with Marplan and for which the incidence in patients treated with Marplan was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in 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, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The commonly observed adverse event that occurred in Marplan patients with an incidence of 5% or greater and at least twice the incidence in placebo patients were nausea, dry mouth, and dizziness (see Table).

In three clinical trials for which the data were pooled, 4 of 85 (5%) patients who received placebo, 10 of 86 (12%) who received  $< 50$  mg of Marplan per day, and 1 of 52 (2%) who received  $\geq 50$  mg of Marplan per day prematurely discontinued treatment. The most common reasons for discontinuation were dizziness, orthostatic hypotension, syncope, and dry mouth.

**Treatment-Emergent Adverse Events Incidence in Placebo-Controlled Clinical Trials  
with Marplan Doses of 40 to 80 mg/day<sup>1</sup>**

BODY SYSTEM/ ADVERSE EVENT	PLACEBO (N=85)	MARPLAN <50 mg (N=86)	MARPLAN $\geq 50$ mg (N=52) <sup>2</sup>
<b>MISCELLANEOUS</b>			
Drowsy	0	4%	0%
Anxiety	1	2%	0%
Chills	0%	2%	0%
Forgetful	1%	2%	2%
Hyperactive	0%	2%	0%
Lethargy	0%	2%	2%
Sedation	1%	2%	0%
Syncope	0%	2%	0%
<b>INTEGUMENTARY</b>			
Sweating	0%	2%	2%
<b>MUSCULOSKELETAL</b>			
Heavy feeling	0%	2%	0%
<b>CARDIOVASCULAR</b>			
Orthostatic hypotension	1%	4%	4%
Palpitations	1%	2%	0%
<b>GASTROINTESTINAL</b>			
Dry mouth	4%	9%	6%
Constipation	6%	7%	4%
Nausea	2%	6%	4%
Diarrhea	1%	2%	0%
<b>UROGENITAL</b>			
Impotence	0%	2%	0%
Urinary frequency	1%	2%	0%
Urinary hesitancy	0%	1%	4%
<b>CENTRAL NERVOUS SYSTEM</b>			
Headache	13%	15%	6%
Insomnia	4%	4%	6%
Sleep disturbance	0%	5%	2%
Tremor	0%	4%	4%
Myoclonic jerks	0%	2%	0%
Paresthesia	1%	2%	0%
<b>SPECIAL SENSES</b>			
Dizziness	14%	29%	15%

<sup>1</sup>Events reported by at least 1% of patients treated with Marplan are presented, except for those that had an incidence on placebo greater than or equal to that on Marplan.

<sup>2</sup>All patients also received Marplan at doses  $< 50$  mg.

## MARPLAN<sup>®</sup> (isocarboxazid)

**Other Events Observed During the Postmarketing Evaluation of Marplan:** Isolated cases of akathisia, ataxia, black tongue, coma, dysuria, euphoria, hematologic changes, incontinence, neuritis, photosensitivity, sexual disturbances, spider telangiectases, and urinary retention have been reported. These side effects sometimes necessitate discontinuation of therapy. In rare instances, hallucinations have been reported with high dosages, but they have disappeared upon reduction of dosage or discontinuation of therapy. Toxic amblyopia was reported in one psychiatric patient who had received isocarboxazid for about a year; no causal relationship to isocarboxazid was established. Impaired water excretion compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported.

**DRUG ABUSE AND DEPENDENCE: Controlled Substance Class:** Marplan is not a controlled substance.

**Physical and Psychological Dependence:** Marplan has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. There have been reports of drug dependency in patients using doses of Marplan significantly in excess of the therapeutic range. Some of these patients had a history of previous substance abuse. The following withdrawal symptoms have been reported: restlessness, anxiety, depression, confusion, hallucinations, headache, weakness, and diarrhea. Consequently, physicians should carefully evaluate Marplan patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

**OVERDOSAGE:** The lethal dose of Marplan in humans is not known. There has been one report of a fatality in a patient who ingested 400 mg of Marplan together with an unspecified amount of another drug. Symptoms: Major overdosage may be evidenced by tachycardia, hypotension, coma, convulsions, respiratory depression, sluggish reflexes, pyrexia, and diaphoresis; these signs may persist for 8 to 14 days. Treatment: General supportive measures should be used, along with immediate gastric lavage or emetics. If the latter are given, the danger of aspiration must be borne in mind. An adequate airway should be maintained, with supplemental oxygen if necessary. The mechanism by which amine-oxidase inhibitors produce hypotension is not fully understood, but there is evidence that these agents block the vascular bed response. Thus it is suggested that plasma may be of value in the management of this hypotension. Administration of pressor amines such as Levophed<sup>®</sup> (levarterenol bitartrate) may be of limited value (note that their effects may be potentiated by Marplan). Continue treatment for several days until homeostasis is restored. Liver function studies are recommended during the 4 to 6 weeks after recovery, as well as the time of overdosage.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

**DOSAGE AND ADMINISTRATION:** For maximum therapeutic effect, the dosage of Marplan must be individually adjusted on the basis of careful observation of the patient. Dosage should be started with one tablet (10 mg) of Marplan twice daily. If tolerated, dosage may be increased by increments of one tablet (10 mg) every 2 to 4 days to achieve a dosage of four tablets daily (40 mg) by the end of the first week of treatment. Dosage can then be increased by increments of up to 20 mg/week, if needed and tolerated, to a maximum recommended dosage of 60 mg/day. Daily dosage should be divided into two to four dosages. After maximum clinical response is achieved, an attempt should be made to reduce the dosage slowly over a period of several weeks without jeopardizing the therapeutic response. Beneficial effect may not be seen in some patients for 3 to 6 weeks. If no response is obtained by then, continued administration is unlikely to help.

Because of the limited experience with systematically monitored patients receiving Marplan at the higher end of the currently recommended dose range of up to 60 mg/day, caution is indicated in patients for whom a dose of 40 mg/day is exceeded (see ADVERSE REACTIONS).

**HOW SUPPLIED:** Tablets, 10 mg isocarboxazid each, peach-colored, scored—bottles of 100 (NDC 30698-032-01).

**RX only.**

## 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 antidepressant?

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 yourself 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 risk 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 takes an antidepressant

#### 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

## MARPLAN<sup>®</sup> (isocarboxazid)

- 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 symptoms.

#### 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<sup>™</sup>)<sup>\*</sup> has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac<sup>™</sup>)<sup>\*</sup>, sertraline (Zoloft<sup>™</sup>)<sup>\*</sup>, fluvoxamine, and clomipramine (Anafranil<sup>™</sup>)<sup>\*</sup>.

Your healthcare provider may suggest other antidepressants based on the past experience of your 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.

\*Prozac<sup>™</sup> is a registered trademark of Eli Lilly & Company

\*Zoloft<sup>™</sup> is a registered trademark of Pfizer Pharmaceuticals

\*Anafranil<sup>™</sup> is a registered trademark of Mallinckrodt Inc.

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



**Manufactured by Amneal Pharmaceuticals, Paterson,  
New Jersey 07504 for  
Validus Pharmaceuticals, Inc.  
Parsippany, New Jersey 07054**

**Revised: May 2007**

**Printed in U.S.A.**