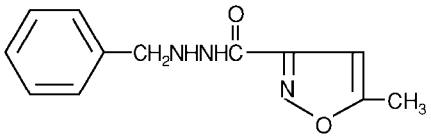
# ATTACHMENT

# FINAL LABELING

**MARPLAN®**
**brand of isocarboxazid**
**TABLETS**

## DESCRIPTION

Marplan (isocarboxazid), a monoamine oxidase inhibitor, is available for oral administration in 10-mg tablets. Each tablet also contains gelatin, lactose, magnesium stearate, corn starch, talc, FD&C Red No. 3 and FD&C Yellow No. 6. 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 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, buproprion 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.

Patients with Severe/Frequent Headaches

Patients with severe or frequent headaches should not be considered candidates for therapy with Marplan, because headaches during therapy may be the first symptom of a hypertensive reaction to the drug.

**Contraindicated MAOI-Other Drug Combinations**

Other MAO 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)** |
|---|---|
| **Other MAO Inhibitors** | |

| | |
|---|---|
| Furazolidone | Furoxone® (Roberts Laboratories) |
| Pargyline HCL | Eutonyl® (Abbott Laboratories) |
| Pargyline HCL and methyclothiazide | Eutron® (Abbott Laboratories) |
| Phenelzine sulfate | Nardil® (Parke-Davis) |
| Procarbazine | Matulane® (Roche Laboratories) |
| Tranylcypromine sulfate | Parnate® (SmithKline Beecham Pharmaceuticals) |

**Dibenzazepine-Related and Other Tricyclics**

| | |
|---|---|
| Amitriptyline HCL | Elavil® (Zeneca) |
| | Endep® (Roche Products) |
| Perphenazine and amitriptyline HCL | Etrafon® (Schering) |
| | Triavil® (Merck Sharp & Dohme) |
| Clomipramine hydrochloride | Anafranil® (Novartis) |
| Desipramine HCL | Norpramin® (Hoechst Marion Roussel) |
| | Pertofrane® (Rhône-Poulenc Rorer Pharmaceuticals) |
| Imipramine HCL | Janimine® (Abbott Laboratories) |
| | Tofranil® (Novartis) |
| Nortriptyline HCL | Aventyl® (Eli Lilly & Co.) |
| | Pamelor® (Novartis) |
| Protripyline 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 | Ludiomil® (Novartis) |
| Trimipramine maleate | Surmontil® (Wyeth-Ayerst Laboratories) |

Bupropion

The concurrent administration of an MAO inhibitor and bupropion hydrochloride (Wellbutrin® and Zyban®, 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 an 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.

Buspirone

Marplan should not be used in combination with buspirone HCL (Buspar®, Bristol-Myers Squibb); several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCL. At least 10 days should elapse between the discontinuation of Marplan and the institution of buspirone HCL.

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, methyldopa, 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

### 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 crises, phentolamine (available as Regitine®, Novartis) has been used and is recommended at a dosage of 5 mg I.V. 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**

**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.

Lowered 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, others 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.

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 glycemic 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® (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 ≥50 mg/day, including only 11 who were dosed at ≥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 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, 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 ≥ 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[1]

| Body System/ Adverse Event | PLACEBO (N=85) | MARPLAN <50 mg (N=86) | MARPLAN ≥50 mg (N=52)[2] |
|---|---|---|---|
| MISCELLANEOUS | | | |
| 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% |
| INTEGUMENTARY | | | |
| Sweating | 0% | 2% | 2% |
| MUSCULOSKELETAL | | | |
| Heavy feeling | 0% | 2% | 0% |
| CARDIOVASCULAR | | | |
| Orthostatic hypotension | 1% | 4% | 4% |
| Palpitations | 1% | 2% | 0% |
| GASTROINTESTINAL | | | |
| Dry mouth | 4% | 9% | 6% |
| Constipation | 6% | 7% | 4% |
| Nausea | 2% | 6% | 4% |
| Diarrhea | 1% | 2% | 0% |
| UROGENITAL | | | |
| Impotence | 0% | 2% | 0% |
| Urinary frequency | 1% | 2% | 0% |
| Urinary hesitancy | 0% | 1% | 4% |
| CENTRAL NERVOUS | | | |
| 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% |
| SPECIAL SENSES | | | |
| Dizziness | 14% | 29% | 15% |

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

2 All patients also received Marplan at doses 50 mg.

**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® (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 at 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 doses. 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 0004-0032-01).

Rx only

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Printed in U.S.A.

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