ISOCARBOXAZID

**Brands** • Marplan
*see index for additional brand names*

**Generic?** Not in USA

**Class**
- Neuroscience-based Nomenclature: serotonin, norepinephrine, dopamine enzyme inhibitor (SN-EI)
- Monoamine oxidase inhibitor (MAOI)

**Commonly Prescribed for**
*bold for FDA approved*
- Depression
- Treatment-resistant depression
- Treatment-resistant panic disorder
- Treatment-resistant social anxiety disorder

**How the Drug Works**
- Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, and dopamine
- This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission

**How Long Until It Works**
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms

**If It Works**
- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission)
- Once symptoms are gone, continue treating for 1 year for the first episode of depression

**If It Doesn’t Work**
- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Augmentation of MAOIs has not been systematically studied, and this is something for the expert, to be done with caution and with careful monitoring
- A stimulant such as d-amphetamine or methylphenidate (with caution; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)
- Lithium
- Mood-stabilizing anticonvulsants
- Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)

**Tests**
- Patients should be monitored for changes in blood pressure
- Patients receiving high doses or long-term treatment should have hepatic function evaluated periodically
Life-Threatening or Dangerous Side Effects

- Hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs)
- Induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Seizures
- Hepatotoxicity

Weight Gain

- Many experience and/or can be significant in amount

Sedation

- Many experience and/or can be significant in amount
- Can also cause activation

What to Do About Side Effects

- Wait
- Wait
- Wait
- Lower the dose
- Take at night if daytime sedation
- Switch after appropriate washout to an SSRI or newer antidepressant

Best Augmenting Agents for Side Effects

- Trazodone (with caution) for insomnia
- Benzodiazepines for insomnia
- Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine
- Many side effects cannot be improved with an augmenting agent

SIDE EFFECTS

How Drug Causes Side Effects

- Theoretically due to increases in monoamines in parts of the brain and body and at receptors other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on vascular smooth muscle causing hypertension, etc.)
- Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

- Dizziness, sedation, headache, sleep disturbances, fatigue, weakness, tremor, movement problems, blurred vision, increased sweating
- Constipation, dry mouth, nausea, change in appetite, weight gain
- Sexual dysfunction
- Orthostatic hypotension (dose-related); syncope may develop at high doses

DOSING AND USE

Usual Dosage Range

- 40–60 mg/day
Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine).

Do not combine with another MAOI, alcohol, or guanethidine.

Adverse drug reactions can result from combining MAOIs with tricyclic/tetracyclic antidepressants and related compounds, including carbamazepine, cyclobenzaprine, and mirtazapine, and should be avoided except by experts to treat difficult cases (see Pearls).

MAOIs in combination with spinal anesthesia may cause combined hypotensive effects.

Combination of MAOIs and CNS depressants may enhance sedation and hypotension.

Use requires low tyramine diet (see Table 2 after Pearls).

Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations.

Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls).

Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents.

Isocarboxazid is not recommended for use in patients who cannot be monitored closely.

When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart.

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**Dosage Forms**
- Tablet 10 mg

**How to Dose**
- Initial 10 mg twice a day; increase by 10 mg/day every 2–4 days; dosed 2–4 times/day; maximum dose 60 mg/day

**Dosing Tips**
- Orthostatic hypotension, especially at high doses, may require splitting into 3 or 4 daily doses.
- Patients receiving high doses may need to be evaluated periodically for effects on the liver.
- Little evidence to support efficacy of isocarboxazid at doses below 30 mg/day.

**Overdose**
- Dizziness, sedation, ataxia, headache, insomnia, restlessness, anxiety, irritability; cardiovascular effects, confusion, respiratory depression, or coma may also occur.

**Long-Term Use**
- May require periodic evaluation of hepatic function.
- MAOIs may lose some efficacy long-term.

**Habit Forming**
- Some patients have developed dependence to MAOIs.

**How to Stop**
- Generally no need to taper, as drug wears off slowly over 2–3 weeks.

**Pharmacokinetics**
- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition.

**Drug Interactions**
- Tramadol may increase the risk of seizures in patients taking an MAOI.
- Can cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor or for 5 half-lives after stopping the serotonin reuptake inhibitor (see Table 1 after Pearls).

- Hypertensive crisis with headache, intracranial bleeding, and death may result from combining MAOIs with sympathomimetic drugs (e.g., amphetamines, methylphenidate, cocaine, dopamine, epinephrine, norepinephrine, and related compounds methyldopa, levodopa, L-tryptophan, L-tyrosine, and phenylalanine).
- Do not combine with another MAOI, alcohol, or guanethidine.
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- MAOIs in combination with spinal anesthesia may cause combined hypotensive effects.
- Combination of MAOIs and CNS depressants may enhance sedation and hypotension.

**Other Warnings/Precautions**
- Use requires low tyramine diet (see Table 2 after Pearls).
- Patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations.
- Over-the-counter medications to avoid include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls).
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents.
- Isocarboxazid is not recommended for use in patients who cannot be monitored closely.
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart.
• Distribute the brochures provided by the FDA and the drug companies
• Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
• Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use
• If patient is taking meperidine (pethidine)
• If patient is taking a sympathomimetic agent or taking guanethidine
• If patient is taking another MAOI
• If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
• If patient is taking diuretics, dextromethorphan
• If patient has pheochromocytoma
• If patient has cardiovascular or cerebrovascular disease
• If patient has frequent or severe headaches
• If patient is undergoing elective surgery and requires general anesthesia
• If patient has a history of liver disease or abnormal liver function tests
• If patient is taking a prohibited drug
• If patient is not compliant with a low tyramine diet
• If there is a proven allergy to isocarboxazid

Elderly patients may have greater sensitivity to adverse effects
• Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents
• Not recommended for use in children under age 16
• Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
• Distribute the brochures provided by the FDA and the drug companies
• Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
• Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Not generally recommended for use during pregnancy, especially during first trimester
• Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding
• Some drug is found in mother’s breast milk
• Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated later

SPECIAL POPULATIONS

Renal Impairment
• Use with caution – drug may accumulate in plasma
• May require lower than usual adult dose

Hepatic Impairment
• Not for use in hepatic impairment

Cardiac Impairment
• Contraindicated in patients with congestive heart failure or hypertension
• Any other cardiac impairment may require lower than usual adult dose
• Patients with angina pectoris or coronary artery disease should limit their exertion

Elderly
• Initial dose lower than usual adult dose
females), and isocarboxazid can be used to treat both depression and bulimia
• MAOIs are a viable second-line treatment option in depression, but are not frequently used

✽ Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough
• Orthostatic hypotension, insomnia, and sexual dysfunction are often the most troublesome common side effects

✽ MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)

✽ MAOIs should not be neglected as therapeutic agents for the treatment-resistant
• Although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is for an expert to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
• Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
• Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
• If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
• Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI and tricyclic/tetracyclic combinations may be weight gain and orthostatic hypotension

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Atypical depression
• Severe depression
• Treatment-resistant depression or anxiety disorders

Potential Disadvantages
• Requires compliance to dietary restrictions, concomitant drug restrictions
• Patients with cardiac problems or hypertension
• Multiple daily doses

Primary Target Symptoms
• Depressed mood
• Somatic symptoms
• Sleep and eating disturbances
• Psychomotor retardation
• Morbid preoccupation

Pearls
• MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
• Despite little utilization, some patients respond to isocarboxazid who do not respond to other antidepressants including other MAOIs
• Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions with the MAOI
• Headache is often the first symptom of hypertensive crisis
• The rigid dietary restrictions may reduce compliance (see Table 2 after Pearls)
• Mood disorders can be associated with eating disorders (especially in adolescent
Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

<table>
<thead>
<tr>
<th>Do Not Use:</th>
<th>SSRIs</th>
<th>MDMA (ecstasy)</th>
<th>Meperidine</th>
<th>Non-subcutaneous sumatriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>Cocaine</td>
<td>Tramadol</td>
<td>Chlorpheniramine</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Methamphetamine</td>
<td>Methadone</td>
<td>Brompheniramine</td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>High-dose or injected amphetamine</td>
<td>Fentanyl</td>
<td>Dextromethorphan</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Procarbazine?</td>
</tr>
</tbody>
</table>

Table 2. Dietary guidelines for patients taking MAOIs

<table>
<thead>
<tr>
<th>Foods to avoid*</th>
<th>Foods allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese</td>
</tr>
<tr>
<td>Tap and unpasteurized beer</td>
<td>Canned or bottled beer and alcohol</td>
</tr>
<tr>
<td>Marmite</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Sauerkraut, kimchee</td>
<td></td>
</tr>
<tr>
<td>Soy products/tofu</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Banana peel</td>
<td>Bananas, avocados, raspberries</td>
</tr>
<tr>
<td>Tyramine-containing nutritional supplement</td>
<td></td>
</tr>
</tbody>
</table>

*Not necessary for 6-mg transdermal or low-dose oral selegiline

Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

<table>
<thead>
<tr>
<th>Use With Caution:</th>
<th>Decongestants</th>
<th>Stimulants</th>
<th>Antidepressants with norepinephrine reuptake inhibition</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Amphetamines</td>
<td>Most tricyclics</td>
<td>Phentermine</td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
<td>NRIs</td>
<td>Local anesthetics containing vasoconstrictors</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>NDRIs</td>
<td>Methamphetamine</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Modafinil</td>
<td>Tapentadol</td>
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<td></td>
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<td>Armodafinil</td>
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**Suggested Reading**

