

# Amiodarone

## Uniquely effective, but uniquely toxic

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Amiodarone ([Cordarone](#), [Pacerone](#)) is the most effective, and certainly the strangest, antiarrhythmic drug ever developed. Anyone being treated with amiodarone should understand the idiosyncrasies - and the risks - associated with this highly effective drug.

## Unusual features of amiodarone

Amiodarone has several characteristics that make it unique.

First, the drug takes weeks to achieve its maximum effectiveness. This is because amiodarone is stored in most of the tissues of the body, and to "load" the body with the drug, all the tissues need to be saturated. The typical "loading" regimen of amiodarone, therefore, is to use very large doses for a week or two, then taper the dosage over the next month or so. It is not unusual to give patients 1200 or 1600 mg per day at first, and then maintain them on as little as 100 or 200 mg per day chronically.

Second, amiodarone leaves the body very, very slowly. It is not excreted (like most drugs) by the liver or the kidneys. It is lost when amiodarone-containing human cells are lost - such as skin cells or cells from the GI tract, which are shed by the millions each day. Thus, if it is decided that one needs to stop amiodarone, the drug remains in the body in measurable quantities for months and months. The "half life" of the drug, in contrast to most other drugs, is measured in weeks instead of hours.

Third, because amiodarone is stored in many different kinds of tissues, it can produce side effects affecting many different organs. Some of these side effects take months or years to develop, so it is never true that one can stop being vigilant.

Fourth, amiodarone works through many different mechanisms, unlike most drugs. It fits into two separate categories of antiarrhythmic drugs (Class I and Class III, for what it's worth). It acts as a beta blocker and also as a calcium blocker. It dilates blood vessels, and and it often acts to "block" the effect of thyroid hormone.

## The side effects of amiodarone

The side effects of amiodarone often take weeks or months to develop, so must be watched for as long as the drug is used.

Amiodarone commonly causes deposits to form on the cornea of the eyes - often leading to "halo-vision," where looking at bright lights at night is like looking at the moon on a foggy evening.

Amiodarone can cause a very disfiguring blue-grey discoloration of the skin, generally in areas of sun exposure.

Amiodarone often sensitizes the skin to sunlight, so that even trivial exposure can cause a fairly nasty sunburn.

Amiodarone can cause thyroid disorders, both hypothyroidism (low thyroid) and hyperthyroidism (high thyroid.) These thyroid problems are common with amiodarone, and can be unusually difficult to recognize and treat. For this reason, patients taking this drug should have their thyroid function routinely monitored.

Amiodarone can cause liver toxicity, so liver enzymes need to be monitored periodically. It can also cause rather severe gastric reflux.

The most serious side effect of amiodarone is pulmonary toxicity - lung disease. It can take several forms, from an acute lung syndrome that makes patients desperately ill, requires intensive care, and often results in death, to a more insidious, gradual, unnoticeable, "stiffening" of the lungs that both the doctor and patient can overlook until finally severe, probably irreversible lung damage is done. [You can read more about amiodarone lung toxicity here.](#)

## Amiodarone Lung Toxicity

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Amiodarone ([Cordarone](#), [Pacerone](#)) is the most effective drug yet developed for the treatment of cardiac arrhythmias (heart rhythm disturbances). Unfortunately, it is also potentially the most toxic

antiarrhythmic drug, and the most challenging to use safely. ([Read a general review of amiodarone here.](#)) For this reason, amiodarone should only be used by patients with life-threatening or severely disabling arrhythmias, and who have no other likely treatment options.

The most feared side effect of amiodarone, by far, is pulmonary (lung) toxicity.

## What is Amiodarone Lung Toxicity?

Amiodarone lung toxicity probably affects about 5% of patients taking this drug, and can take at least four forms.

The most dangerous is a sudden, life-threatening, diffuse lung problem called **acute respiratory distress syndrome (ARDS)**. Patients with ARDS rapidly develop severe shortness of breath and difficulty getting sufficient oxygen into the bloodstream. They usually must be placed on mechanical ventilators, and their mortality rate -- even with intensive therapy -- approaches 50%. ARDS related to amiodarone is seen most often following major surgical procedures, especially cardiac surgery, but it can be seen at any time and without any obvious precipitating causes.

More common is a chronic, diffuse lung problem called **interstitial pneumonitis (IP)**. IP usually has an insidious and gradual onset, with slowly progressing shortness of breath, cough and easy fatigue. Since many patients taking amiodarone have a history of heart problems, their symptoms are easy to mistake for heart disease (or sometimes, the effects of aging). For this reason, IP is often missed. It is probably more frequent than generally thought.

Much less common are the "**typical-pattern**" **pneumonias** sometimes seen with amiodarone, in which a chest x-ray shows a localized area of congestion. This form of amiodarone lung toxicity is almost always mistaken for a bacterial pneumonia and is treated accordingly. It is usually only when the pneumonia fails to improve that the diagnosis of amiodarone lung toxicity is considered.

Rarely, amiodarone can produce a **solitary pulmonary mass** that is detected by a chest x-ray. The mass is most often thought to be a tumor or infection, and only when the biopsy is taken is amiodarone lung toxicity finally recognized.

## How is Amiodarone Lung Toxicity Diagnosed?

There are no specific diagnostic tests that clinch the diagnosis, though there are strong clues that can be obtained by examining cells from lung tissue (after a biopsy) or from pulmonary lavage (cells are obtained by placing a tube in the airways and flushing with fluid). The key to diagnosing lung toxicity from amiodarone is to be alert for new pulmonary symptoms in anybody taking amiodarone and, at the first sign of problems, to strongly consider this diagnosis. Unexplained pulmonary conditions for which no other likely cause can be identified should be judged as probable amiodarone lung toxicity, and stopping the drug should be strongly considered. (If you are taking amiodarone and suspect this, speak to your doctor before stopping the drug on your own.)

## Who Is At Risk?

Anybody taking amiodarone is at risk. People on higher doses (400 mg per day or more) and people who have been taking the drug for a long time appear to have a higher risk, and some evidence suggests that individuals with underlying lung disease are also more likely to have problems with amiodarone. While chronically monitoring patients on amiodarone with chest x-rays and pulmonary

function tests often reveals changes attributable to the drug, few of these patients go on to develop frank illness. So such monitoring is not useful in detecting who will develop lung toxicity, or who ought to stop taking amiodarone because of "impending" lung toxicity.

## How is Amiodarone Lung Toxicity Treated?

There is no specific therapy that has been shown to be effective. The mainstay of treatment is stopping amiodarone. Unfortunately, it takes many months to rid the body of amiodarone after the last dose. For most patients with the less severe forms of lung toxicity (IP, typical pneumonia, or pulmonary mass), however, the lungs often eventually improve if the drug is stopped. Amiodarone should also be stopped patients with ARDS, but in this case, the patients' ultimate clinical outcome is almost always determined well before amiodarone levels can be significantly reduced. High doses of steroids are most often given to patients with amiodarone-induced ARDS, and while there are case reports of benefit from such therapy, whether steroids actually make a significant difference is unknown.

## The Bottom Line

There are good reasons that amiodarone lung toxicity is the most feared complication. It is unpredictable. It can be severe and even fatal. It can be a challenge to diagnose, and there is no specific therapy to treat it. Even if lung toxicity were the only significant side effect of amiodarone ([which it decidedly is not](#)), this alone should be enough to make clinicians reluctant to use this drug except when absolutely necessary.

### Sources

Dusman, RE, Stanton, MS, Miles, WM, et al. Clinical features of amiodarone-induced pulmonary toxicity. [Circulation](#) 1990; 82:51.

## Interactions with other drugs

The [pharmacokinetics](#) of numerous [drugs](#), including many that are commonly administered to individuals with [heart](#) disease, are affected by amiodarone. Particularly, doses of [digoxin](#) should be halved in individuals taking amiodarone.

Amiodarone potentiates the action of [warfarin](#). Individuals taking both of these medications should have their warfarin dose halved and their anticoagulation status (measured as [prothrombin time](#) (PT) and [international normalized ratio](#) (INR)) measured more frequently. The effect of amiodarone in the warfarin concentration can be as early as a few days after initiation of treatment, or can be delayed a few weeks.

Amiodarone inhibits the action of the [cytochrome P450 isozyme](#) family. This reduces the clearance of many drugs, including the following: -

[Cyclosporine](#)

[Digoxin](#)

[Flecainide](#)

[Procainamide](#)

[Quinidine](#)

[Sildenafil](#)

[Simvastatin](#)

[Theophylline](#)

[Warfarin](#)

### [[edit](#)] **Excretion**

Unlike most other [drugs](#), which are excreted via the [urine](#), excretion is primarily hepatic and biliary with almost no elimination via the renal route and it is not dialyzable [Package Insert- Pacerone(R)]. Elimination half-life average of 58 days (ranging from 25-100 days [Remington: The Science and Practice of Pharmacy 21st edition]) for amiodarone and 36 days for the active metabolite, desethylamiodarone (DEA) [Package Insert- Pacerone(R)]. There is 10-50% transfer of amiodarone and DEA in the placenta as well as presence in breast milk [Package Insert- Pacerone(R)]. Accumulation of amiodarone and DEA occurs in adipose tissue and highly perfused organs (ie. liver, lungs) [Package Insert- Pacerone(R)], therefore, if an individual was taking amiodarone on a chronic basis, if it is stopped it will remain in the system for weeks to months.