

# Amiodarone brand-change and a reminder on patient monitoring

## KEY POINTS

- Cordarone-X will be the sole subsidised brand of amiodarone from 1 January, 2017
- Regular monitoring is necessary for patients taking amiodarone as adverse effects are common and potentially serious, including pulmonary and hepatic toxicity and thyroid dysfunction; it is reported that up to 20% of patients withdraw from amiodarone treatment due to adverse effects
- Pulmonary toxicity occurs in up to 5% of patients taking amiodarone and should be suspected in all patients who present with new or worsening pulmonary symptoms

## Advise patients taking amiodarone of an upcoming brand change

Two brands of amiodarone are currently subsidised in New Zealand; Aratac (a generic brand) and Cordarone-X (the innovator brand). From 1 October, 2016, there may be a part payment required for the Aratac brand while Cordarone-X will continue to be fully subsidised. From 1 January, 2017, Cordarone-X will be the sole subsidised brand of amiodarone

and the Aratac brand will be delisted from the Pharmaceutical Schedule.

Amiodarone is prescribed to approximately 6400 patients\* in New Zealand each year. Approximately 20% of these patients are taking the Aratec brand and will need to switch to Cordarone-X to continue to receive fully subsidised treatment.<sup>1</sup>


\* Amiodarone was dispensed to 6372 patients between July, 2015 and June, 2016.


## Reassure patients that different brands have the same clinical effect

Patients can be reassured that the safety and effectiveness of all medicines is evaluated by the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) prior to their use in New Zealand. Generic brands need to demonstrate bioequivalence to the innovator brands according to internationally recognised standards. In most cases this is relevant when patients switch from an innovator brand to a generic medicine, but also applies when the switch is from a generic to the innovator brand, i.e. from Aratac to Cordarone-X. It is not expected that there will be a decrease in effectiveness

or different adverse effects when a patient switches between generic and innovator brands of the same medicine.

Both brands of amiodarone are white, circular tablets, but Cordarone-X tablets are slightly bigger in diameter.

 For further information on bioequivalence see: "Generics SE", BPJ (May, 2009).

 Information for patients on generic medicines is available from: [www.pharmac.govt.nz/assets/factsheet-generic-meds.pdf](http://www.pharmac.govt.nz/assets/factsheet-generic-meds.pdf)

## The pharmacology of amiodarone

Amiodarone is an anti-arrhythmic medicine.<sup>2</sup> When initiated, a loading dose is required to reduce the time taken for amiodarone to have a clinical effect.<sup>4</sup> Amiodarone has a half-life between 14 and 59 days in patients taking it long-term.<sup>3</sup> This is due to lipid binding and accumulation in peripheral tissues acting as a reservoir.<sup>4</sup> Amiodarone toxicity may occur due to deposition in the lungs, liver, heart, skin, corneal epithelium and peripheral nerves.<sup>4</sup> Amiodarone contains iodine which can inhibit the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and patients may develop hyper- or hypothyroidism.<sup>5</sup> All patients taking amiodarone long-term need to be monitored for the development of adverse effects.

## Prescribing amiodarone


Amiodarone is typically initiated in secondary care. It is indicated for the treatment of patients with supraventricular or ventricular arrhythmias, atrial fibrillation and flutter, and tachyarrhythmias associated with Wolff-Parkinson-White syndrome.<sup>2</sup>

Amiodarone is contraindicated in patients with sinus bradycardia, sino-atrial heart block, and thyroid dysfunction, unless the patient is in cardiac arrest.<sup>2</sup> In patients with severe conduction disturbances or sinus node disease, amiodarone should be avoided unless the patient has a pacemaker.<sup>2</sup> Amiodarone is currently contraindicated in patients with a history of iodine hypersensitivity.<sup>2</sup> There is, however, little evidence of cross-reactivity with other iodinated compounds such as radiocontrast media.<sup>6</sup> Oral amiodarone is generally prescribed in adults as follows:<sup>2</sup>

- A loading dose of 200 mg, three times daily, for one week
- Reduced to 200 mg, twice daily, for a further week
- A maintenance dose of 200 mg daily or the minimum required for arrhythmia control

When amiodarone is commenced, ensure the patient understands that the loading dose is taken **only** for the initiation period, so that high-dose amiodarone is not inadvertently continued long-term. Check that baseline monitoring (Table 1) has been completed; some baseline testing may need to be

arranged in primary care. It is useful to set reminders for follow-up in the patient's notes. The expected duration of treatment should also be entered in the notes, so that amiodarone is not continued in the community beyond what was intended in secondary care.

 Further prescribing information for amiodarone is available from: [www.nzf.org.nz/nzf\\_1090](http://www.nzf.org.nz/nzf_1090)

## A reminder of the importance of monitoring

Monitoring of patients taking amiodarone is essential as use of the medicine is associated with pulmonary and hepatic toxicity and thyroid dysfunction (Table 1).<sup>3</sup> The reported prevalence of adverse effects associated with amiodarone is 15% in the first year, and 50% of patients taking amiodarone long-term are expected to experience adverse effects.<sup>4</sup>

## The importance of detecting adverse effects early

Pulmonary toxicity is a potentially serious adverse effect associated with the use of amiodarone.<sup>3</sup> Rarely, acute toxicity occurs, with reported mortality rates as high as 50%.<sup>4</sup> The risk of acute toxicity is elevated in the first hours to days following surgical procedures or pulmonary angiography.<sup>3</sup> In one study, the cumulative incidence of pulmonary toxicity in patients taking amiodarone long-term was found to be 4% at one year, 8% at three years and 11% at five years.<sup>7</sup> The pathophysiology of this process is not completely understood, although it does appear to be dose-related.<sup>4</sup>

Risk factors for amiodarone-induced pulmonary toxicity include:<sup>3</sup>

- Daily doses greater than 400 mg
- Treatment duration greater than two months
- Male sex
- Age over 60 years
- Pre-existing lung disease

Amiodarone pulmonary toxicity can cause pneumonitis, interstitial lung disease or respiratory distress.<sup>4</sup> Patients with amiodarone-induced pulmonary toxicity may present with:<sup>3</sup>

- Non-productive cough
- Dyspnoea
- Fever
- Pleuritic chest pain
- Fatigue
- Weight loss

Pulmonary toxicity should be suspected and investigated in all patients taking amiodarone who develop new or worsening pulmonary symptoms.<sup>3</sup> Pulmonary toxicity is a diagnosis of exclusion and other conditions including heart failure, infectious pneumonia, pulmonary embolism and malignancy should also

**Table 1:** Recommended testing for patients before and during treatment with amiodarone<sup>3</sup>

Test	Baseline	Repeat
Liver function tests (ALT and AST)	Yes	Every six months
Thyroid function test (TSH)	Yes	Every six months
Chest X-ray	Yes	Annually
Pulmonary function test, including diffusing capacity of lung for carbon monoxide (DLCO)	Yes	For investigation of: <ul style="list-style-type: none"> <li>■ Unexplained cough or dyspnoea; especially if lung disease is present</li> <li>■ X-ray abnormalities</li> <li>■ Suspected pulmonary toxicity</li> </ul>
Electrocardiogram*	Yes	Annually <sup>4</sup> or as clinically appropriate
Ophthalmological evaluation	If visual impairment is present	If visual symptoms develop
High resolution CT scan	No	If pulmonary toxicity suspected

\* Assess patients for ECG changes such as sinus bradycardia, Q-T prolongation or heart block.

be considered.<sup>3</sup> Infiltrates on chest X-ray and a reduction of more than 20% in the diffusing capacity of the lung for carbon monoxide (DLCO) is highly suggestive of amiodarone-induced pulmonary toxicity.<sup>3</sup> Withdrawal of amiodarone may increase the risk of serious arrhythmias, so it is important to be as certain as possible of the diagnosis. Discussion with a cardiologist is recommended before withdrawing treatment, particularly for patients with life-threatening arrhythmias.

### Managing patients with amiodarone-induced pulmonary toxicity

Adverse pulmonary effects due to amiodarone are reversible in most patients upon withdrawal of the medicine.<sup>8</sup> Due to the long half-life of amiodarone symptoms may be slow to resolve or even initially worsen following withdrawal.<sup>3</sup> Oral corticosteroids are generally recommended for 4 – 12 months to help improve symptoms and prevent relapse.<sup>9</sup> In patients with lung parenchyma involvement, treatment with corticosteroids is reportedly associated with earlier recovery and decreased parenchymal fibrosis.<sup>9</sup> A slow withdrawal of corticosteroids over two to six months is recommended to prevent rebound toxicity.<sup>3</sup>


### Changes in thyroid function may occur

Hyperthyroidism or hypothyroidism, may occur in patients taking amiodarone.<sup>2</sup> Amiodarone can interfere with thyroid function due to iodine in the medicine blocking the conversion of T4 to T3. A 200 mg tablet of amiodarone will yield approximately 40 times the recommended 150 microgram daily intake of iodine in a patient in steady state

metabolism.<sup>5,10</sup> Altered thyroid function tests in the first three months of treatment are common.<sup>4</sup>

Hyperthyroidism is reported to be the most frequent amiodarone-induced adverse effect in New Zealand recorded by the Centre for Adverse Reaction Monitoring (CARM).<sup>8</sup> This can develop rapidly and patients may present with a new arrhythmia.<sup>8</sup> If patients taking amiodarone develop tachycardia or atrial fibrillation their thyroid function should be retested.<sup>8</sup> If a patient has elevated T3 and T4 levels with very low or undetectable TSH levels this is consistent with thyrotoxicosis and amiodarone should be temporarily withdrawn.<sup>8</sup> Carbimazole may be initiated to block thyroid hormone synthesis while amiodarone is excreted.<sup>8</sup> Thyrotoxicosis can take a number of years to develop and patients may not display goitre or ophthalmopathy.<sup>8</sup>

Referral to an endocrinologist is recommended if hypothyroidism develops.<sup>8</sup> This adverse effect does not appear to be dose-related.<sup>8</sup> Patients who are taking amiodarone who develop hypothyroidism can often be managed with levothyroxine while amiodarone is continued.<sup>4</sup>

 Further information on thyroid dysfunction is available from: “Management of thyroid dysfunction in adults”, BPJ 33 (Dec, 2010).

### Other adverse effects associated with amiodarone

**Cornea microdeposits develop in almost all patients** taking amiodarone for longer than six months.<sup>4</sup> Generally, these do not affect visual acuity and treatment can be continued.<sup>4</sup> Optic neuritis and atrophy with vision loss are more serious

adverse effects and ophthalmic examination is recommended if patients develop a visual deficit.<sup>4</sup>

**Photosensitivity reactions are relatively common** in patients taking amiodarone. The severity of any sensitivity may vary, with some patients experiencing intense burning.<sup>8</sup> Patients should be advised to use sunscreen and to wear protective clothing during summer months. A marked bluish-grey skin discolouration, also known as “blue man” or “smurf” syndrome, occurs in a small number of patients (< 3%) taking amiodarone long-term.<sup>11</sup> This reaction is usually associated with long-term, high-dose amiodarone and a case report suggests this discolouration will resolve within a year if the total daily dose is reduced to 200 mg per day in combination with sun protection.<sup>11</sup>

**Bradycardia and torsade de pointes may occur** in patients taking amiodarone.<sup>4</sup> If patients have a cardioverter defibrillator, treatment with amiodarone may increase the cycle length of ventricular tachycardia and interfere with the device’s effectiveness.<sup>4</sup>


**Hepatitis and liver cirrhosis have been reported in patients** taking amiodarone.<sup>4</sup> An increase in liver enzymes is initially expected and treatment can generally be continued unless liver function testing shows an elevation more than two to three times the normal value.<sup>4</sup>

## References

1. Ministry of Health. Pharmaceutical Claims Collection. 2016.
2. New Zealand Formulary (NZF). NZF v48. 2016. Available from: [www.nzf.org.nz](http://www.nzf.org.nz) (Accessed Aug, 2016)
3. Medsafe. Amiodarone pulmonary toxicity - early recognition is vital. Prescr Update;34:38–9.
4. Merino J L, Perez L. Treatment with amiodarone: how to avoid complications. E-J Cardiol Pract 2011;10. Available from: [www.escardio.org/Guidelines-&-Education/Journals-and-publications/ESC-journals-family/E-journal-of-Cardiology-Practice/Volume-10/Treatment-with-amiodarone-How-to-avoid-complications](http://www.escardio.org/Guidelines-&-Education/Journals-and-publications/ESC-journals-family/E-journal-of-Cardiology-Practice/Volume-10/Treatment-with-amiodarone-How-to-avoid-complications) (Accessed Sep, 2016)
5. Sanofi-Aventis New Zealand limited. Data sheet: CORDARONE X. 2015. Available from: [www.medsafe.govt.nz/profs/datasheet/c/CordaroneXtabinj.pdf](http://www.medsafe.govt.nz/profs/datasheet/c/CordaroneXtabinj.pdf)
6. Lakshmanadoss U, Lindsley J, Glick D, et al. Incidence of amiodarone hypersensitivity in patients with previous allergy to iodine or iodinated contrast agents. Pharmacotherapy 2012;32:618–22. doi:10.1002/j.1875-9114.2012.01094.x
7. Yamada Y, Shiga T, Matsuda N, et al. Incidence and predictors of pulmonary toxicity in Japanese patients receiving low-dose amiodarone. Circ J 2007;71:1610–6.
8. Waitemata DHB. Amiodarone - safe prescribing - keep an eye on it. 2013. Available from: [www.saferx.co.nz/full/amiodarone.pdf](http://www.saferx.co.nz/full/amiodarone.pdf) (Accessed Aug, 2016)
9. Nacca N, Bhamidipati CM, Yuhico LS, et al. Severe amiodarone induced pulmonary toxicity. J Thorac Dis 2012;4:667–70. doi:10.3978/j.issn.2072-1439.2012.06.08
10. Ministry of Health (MOH). Nutrient reference values for Australia and New Zealand. 2005. Available from: [www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/n35.pdf?](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n35.pdf?) (Accessed Aug, 2016)
11. Jolly U, Klein G. Blue man syndrome. CMAJ 2016;188:604. doi:10.1503/cmaj.150393
12. U.S. Food and Drug Administration. FDA Drug Safety Communication: Revised dose limitation for Zocor (simvastatin) when taken with amiodarone. 2011. Available from: [www.fda.gov/Drugs/DrugSafety/ucm283137.htm](http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm) (Accessed Sep, 2016)

## Amiodarone may interact with numerous medicines

The potential for medicine interactions should be checked when initiating amiodarone or a new medicine in a patient already taking amiodarone.

 The New Zealand Formulary (NZF) interaction checker is available from: [www.nzf.org.nz/nzf\\_1090](http://www.nzf.org.nz/nzf_1090)

Several interactions with amiodarone of note include:<sup>2</sup>

- Amiodarone should generally be avoided in patients concurrently taking another medicine which may cause QT prolongation, e.g. citalopram, erythromycin, ondansetron, digoxin, or sofosbuvir or ledipasvir + sofosbuvir for the treatment of hepatitis C
- Concurrent use of simvastatin or atorvastatin may increase the risk of myopathy; the dose of simvastatin should not exceed 20 mg per day in patients taking amiodarone.<sup>12</sup> Pravastatin does not interact with amiodarone.

- Interactions between beta blockers and amiodarone may increase cardiac depression and this combination should be prescribed with caution, although in some patients this may be beneficial. If a patient is taking these medicines their potassium levels should be monitored closely.
- The anticoagulant effect of dabigatran can be potentiated by the concurrent use of amiodarone, although dabigatran does not appear to affect the pharmacokinetics of amiodarone.
- Warfarin may have an increased anticoagulant effect in patients taking amiodarone. INR levels should be monitored weekly until a steady state is achieved.
- Grapefruit juice inhibits the metabolism of amiodarone and regular consumption should be avoided in patients taking amiodarone