

Antiarrhythmic medicine brand changes: flecainide and amiodarone

Patients taking oral flecainide or amiodarone need to know that the suppliers of these medicines have changed and that they may notice slight differences in the appearance of their capsules or tablets. General practitioners and community pharmacists can manage the transition to the newly subsidised brands of these medicines by providing reassurance and education.

KEY PRACTICE POINTS:

- Inform patients taking flecainide or amiodarone tablets or capsules* that the brand of these medicines has changed, and they may notice small differences in the appearance of their medicine, but the active ingredient is unchanged:
 - From 1 July, 2019, Flecainide (Teva) 100 mg and 200 mg controlled release capsules are funded alongside the currently funded Tambocor CR, and will be the sole funded brand from 1 December, 2019
 - From 1 September, 2019, Flecainide BNM (50 mg immediate release tablets) will be funded alongside the currently funded Tambocor, and will be the sole funded brand from 1 February, 2020
 - From 1 July, 2019, the Aratac brand of amiodarone (100 mg and 200 mg tablets) is funded alongside the currently funded Cordarone-X, and will be the sole funded brand from 1 December, 2019
- Health professionals in primary care will need to provide patients with reassurance and education that the change will not affect the quality or supply of their medicine; a flecainide brand switch fee is available for pharmacists
- Additional monitoring is not generally required when changing brands of flecainide or amiodarone if the dose is unchanged and the patient is not symptomatic. If a patient requires flecainide plasma monitoring during the brand change that results in an additional consultation PHARMAC will cover the cost of this consultation.

* There is no change to injectable and oral liquid forms of flecainide and amiodarone

Flecainide capsules and tablets need to be changed to continue to be funded

Flecainide is a Class I antiarrhythmic medicine, therefore it slows cardiac contraction by blocking sodium channels.¹ Flecainide is typically initiated in secondary care for rhythm control in people with atrial fibrillation but it is also used for other arrhythmias (for details see: nzf.org.nz/nzf_1096).² Prescriptions of flecainide need to be endorsed by a specialist (including vocationally registered general practitioners). Flecainide is usually initiated at a low dose which is increased according to clinical response with close monitoring of the patient until the maintenance dose is achieved.

The funded brands of controlled and immediate release flecainide are changing

Previously, the only brand of flecainide controlled release capsules (100 mg and 200 mg) that was funded in New Zealand was Tambocor CR. There are approximately 6,200 patients taking flecainide controlled release capsules in New Zealand.³

- **From 1 July, 2019, Flecainide (Teva) controlled release 100 mg and 200 mg capsules are funded and will replace Tambocor CR** over a five-month transition period.⁴
- **From 1 December, 2019, Flecainide (Teva) will be the only funded brand of controlled release flecainide** (until at least 30 June, 2022) and Tambocor CR will not be funded.

Currently, the only brand of flecainide immediate release tablets (50 mg) that is funded in New Zealand is Tambocor. There are approximately 1,600 patients taking flecainide immediate release tablets in New Zealand.

- **From 1 September, 2019, Flecainide BNM 50 mg immediate release tablets will be funded and will replace Tambocor** over a five-month transition period.⁴
- **From 1 February, 2020, Flecainide BNM will be the only funded brand of flecainide 50 mg tablets** (until at least 30 June, 2022) and Tambocor will not be subsidised.

Flecainide immediate release is occasionally extemporaneously compounded as an oral liquid; PHARMAC is currently working with the manufacturer of Flecainide BNM and stakeholders to ensure that this is possible.⁴

A transition period of five months is provided for both flecainide brand changes to allow patients and health professionals adequate time to discuss the change and convert to the new brand.

Plasma and ECG monitoring are not required during a brand change

Patients taking flecainide are monitored frequently by ECG

when treatment is initiated and when doses are increased.¹ Plasma concentration monitoring may also be beneficial for patients with renal or hepatic dysfunction to guide titration of dosing. ECG and plasma monitoring are not required during a flecainide brand change unless the patient is displaying cardiac symptoms or signs that suggest a dose adjustment may be necessary.⁴ If the treating clinician determines that plasma monitoring is advisable, an application to PHARMAC can be made to cover the patient co-payment of one additional consultation per patient for plasma monitoring. Practices can invoice PHARMAC for the General Practitioner co-payment fee in lieu of charging the patient.

 Further information on invoicing for the consultation fee associated with flecainide plasma monitoring is available from: www.pharmac.govt.nz/flecainide (See: "For Health Professionals")

A brand switch fee is available for pharmacists

Community pharmacists also need to provide education and reassurance to people when they change to a different brand of medicine. It will be necessary to stock all subsidised brands of flecainide during the transition period. Community pharmacies will be able to claim a brand switch fee to compensate them for any additional counselling required to successfully transition patients on the first dispensing of the relevant medicine during the following periods:⁴

- 1 December, 2019 to 1 March, 2020 – a brand switch fee will apply for controlled release flecainide capsules
- 1 February, 2020 to 1 May, 2020 – a brand switch fee will apply for immediate release flecainide tablets

 Further information on claiming pharmacy brand switch payments is available from: www.pharmac.govt.nz/assets/pharmacy-claiming-brandswitch.pdf

Reassure patients that the active ingredient is unchanged

Medsafe has approved Flecainide (Teva) using Tambocor CR as the reference medicine and flecainide BNM has been approved with Tambocor as the reference medicine. This means that the newly funded medicines contain the same active ingredient in the same quantity and bioequivalence has been demonstrated with respect to flecainide (see: "Bioequivalence is used to establish the safety of generic medicines"). The only known difference between the newly funded flecainide and the soon to be delisted formulations is that immediate release flecainide BNM does not contain hydrogenated vegetable oil.⁴

There is little difference in the appearance between the newly funded brands of flecainide (Figure 1 – right) and the brands of flecainide that will be delisted (Figure 1 – left).

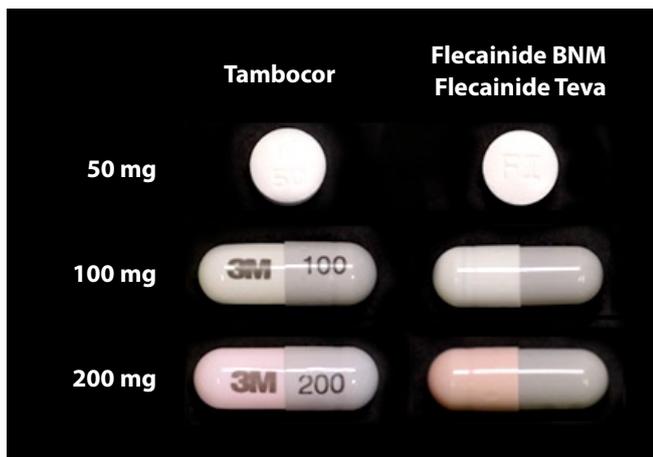


Figure 1: Tambocor immediate release flecainide (50 mg) and Tambocor CR flecainide (100 mg and 200 mg) on the left (soon to be delisted) and newly funded Flecainide BNM (50 mg) and Flecainide (Teva – 100 mg and 200 mg) on the right

Information for patients taking controlled release flecainide information is available from: www.pharmac.govt.nz/assets/2019-flecainide-brand-change-pamphlet-english.pdf

Amiodarone tablets need to be changed to continue to be funded

Amiodarone is classified as a Class III antiarrhythmic medicine as it blocks potassium channels. Amiodarone is typically initiated in secondary care for patients with atrial fibrillation and other tachycardias (for details see: nzf.org.nz/nzf_1090).² Prescriptions of amiodarone need to be endorsed by a specialist (including vocationally registered general practitioners).

Amiodarone is associated with serious adverse effects including pulmonary and hepatic toxicity and thyroid dysfunction.⁵ Regular monitoring in primary care is therefore necessary,⁶ however, additional monitoring is not generally required when patients change brands of amiodarone.

Further information on monitoring patients taking it is available from: www.saferx.co.nz/assets/Documents/ee2548bd3c/amiodarone.pdf

The funded brand of amiodarone is changing

Previously, the only brand of amiodarone capsules (100 mg and 200 mg) that was funded in New Zealand was Cordarone-X. There are approximately 6,900 patients taking amiodarone capsules in New Zealand.³

- **From July 1, 2019, Aratac 100 mg and 200 mg amiodarone tablets are funded and will replace Cordarone-X** over a five-month transition period.⁷
- **From 1 December, 2019, Aratac will be the only funded brand of amiodarone** and Cordarone-X will not be funded.

A transition period of five months is provided to allow patients and health professionals adequate time to discuss the change and convert to the new brand. This brand change is a reversal of one that occurred in January, 2017, when Cordarone-X replaced Aratac as the only funded brand of amiodarone tablets.⁸ Patients who have been taking amiodarone for a number of years will therefore be changing back to the medicine they were originally taking. A brand switch fee will not be available to community pharmacists for the amiodarone transition.

Information for patients

There is very little difference in the appearance of the two brands of amiodarone other than differences in markings and the 100 mg Aratac tablets are slightly bigger than the 100 mg Cordarone-X tablets (Figure 2).



Figure 2: Cordarone-X (100 mg and 200 mg amiodarone) on the left (soon to be delisted) and Aratac (100 mg and 200 mg amiodarone) on the right

Providing patient reassurance during a brand change

A brand change is traditionally thought of as changing to a generic medicine (see below) from an original brand, also referred to as the innovator medicine. However, medicine brands may also be changed from generic to generic and from generic to innovator. A strict regulatory framework exists in New Zealand to ensure that the quality and supply of any medicines undergoing a brand change is not compromised. A generic medicine is required to be bioequivalent to the reference medicine which is usually the innovator brand. Generic medicines cannot be sold until the patent on the innovator medicine has expired. The generic medicines that are approved for use in New Zealand by Medsafe are manufactured according to the same international standards and Good Manufacturing Practice as innovator medicines.⁹

Further information on generic medicines for patients is available from: www.pharmac.govt.nz/assets/factsheet-generic-meds.pdf

Adverse reactions to excipients are extremely rare

Excipients are substances included in medicines to aid in manufacturing, to protect or enhance the stability of the active ingredient or to improve bioavailability or patient acceptability.¹⁰ Manufacturers must supply Medsafe with a list of all the excipients used in their medicines to ensure they are not toxic, are internationally approved and that the risk of adverse reactions is minimal. It is, however, possible for patients to experience an adverse reaction to an excipient.

 All the excipients contained in medicines are listed on the medicine's data sheet, available from: www.medsafe.govt.nz

Ask patients to report any concerns about adverse effects

Adverse effects following a brand change are highly unlikely, however, patients should be advised to report any concerning symptoms. Regarding the flecainide and amiodarone brand changes, if patients report cardiac symptoms, an ECG may provide reassurance to patients and can also detect changes in their condition that are unrelated to the brand change. This is also an opportune time to reinforce to patients taking amiodarone the importance of reporting respiratory symptoms early, e.g. unexplained cough or dyspnoea, as adverse pulmonary effects usually require treatment withdrawal.

Bioequivalence is used to establish the safety of generic medicines

Clinical trials to test the efficacy of the active ingredient of generic medicines are not required as these have already been conducted by the manufacturers of the innovator brands. Manufacturers of generic medicines are instead required to present clinical evidence to Medsafe to demonstrate that the medicine is bioequivalent to the originator brand of medicine or a suitable alternative. Once bioequivalence is demonstrated it is assumed that the medicine will have the same clinical effects.⁹

Bioequivalence studies measure aspects of absorption and blood levels of the active ingredient in no less than 12 healthy volunteers.¹¹ This includes the parameter 'area under the curve' (AUC), which reflects the extent and duration of exposure to the active ingredient, and the parameter maximum plasma concentration (C_{max}).¹¹ It is assumed that if the generic and innovator medicine behaves the same way in healthy people, they will also behave the same way in people with morbidities. The study protocol is randomised and has a cross-over design with a washout period, so each participant is administered the generic and innovator medicine.⁹

Bioequivalence is established if the 90% confidence interval for the ratio of the generic and reference medicines is within the range of 80–125%.¹¹ The actual difference in

exposure to the active ingredient between generics and innovators is less than 5%.⁹ The 80–125% acceptance range is the international standard for demonstrating bioequivalence.¹¹ This range accounts for statistical error and is generally considered to be clinically insignificant.⁹ If a medicine has a narrow therapeutic range, i.e. there is only a small difference between the effective dose and doses which produce unacceptable adverse effects, the acceptance range for bioequivalence reduces to 90–111%.⁹ N.B. Flecainide is an example of a medicine that is considered to have a narrow therapeutic range.¹²

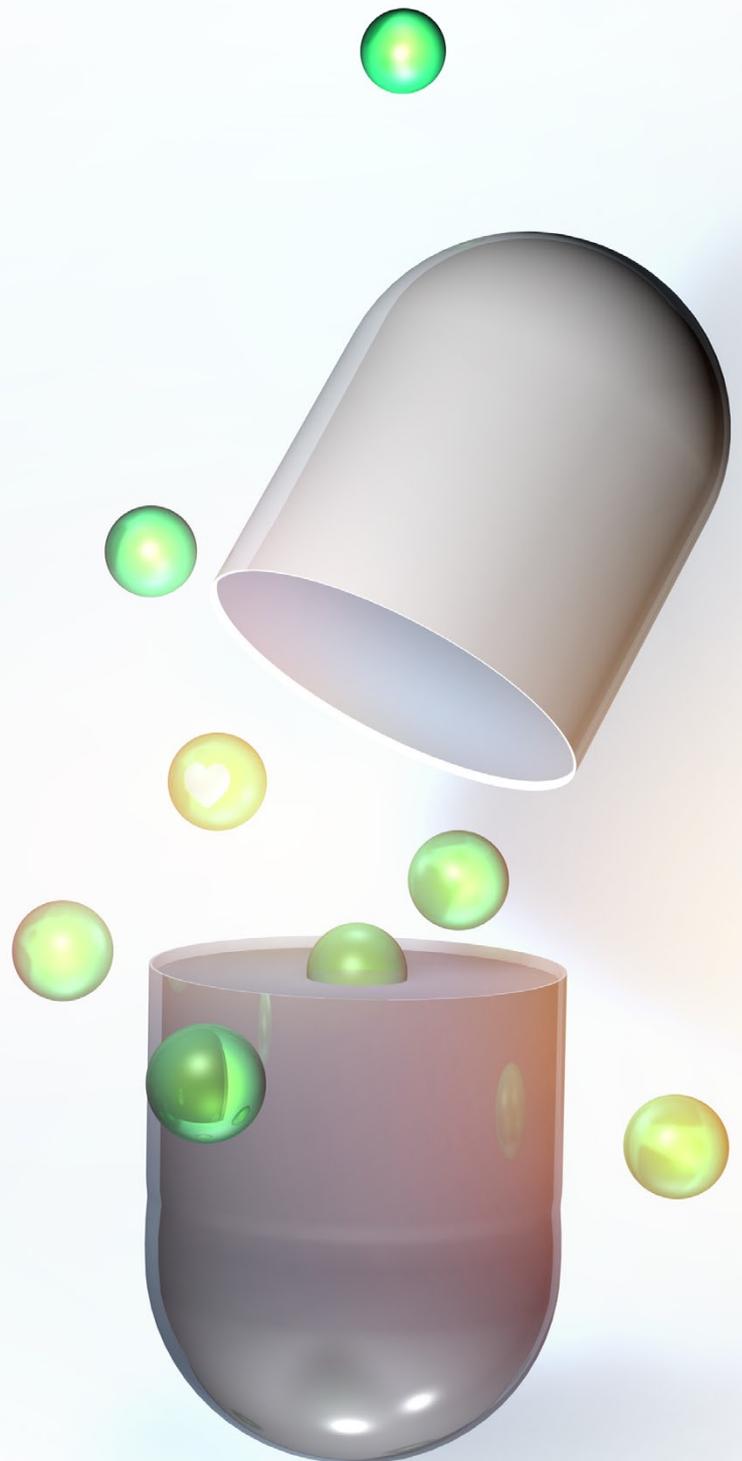
The appropriateness of using bioequivalence as a surrogate for clinical efficacy and safety is supported by numerous studies. A systematic review of 74 studies investigating the efficacy of generic cardiovascular medicines in comparison to branded medicines found no significant difference in clinical outcomes.¹⁴

 Further information on bioequivalence and the approval process for generic medicines is available at: <https://medsafe.govt.nz/profs/PUArticles/Mar2013GenericMedBioequivalence.htm> and www.medsafe.govt.nz/profs/PUArticles/September2017/TheMedsafeFiles4NMAssessment.htm



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