# Transitioning people off Accuretic

## Accuretic is being withdrawn

Accuretic (quinapril 10mg + hydrochlorothiazide 12.5mg and quinapril 20mg + hydrochlorothiazide 12.5mg) is indicated in New Zealand for the treatment of hypertension in patients not adequately controlled with monotherapy.

Pfizer test results have identified the levels of N-nitroso-quinapril exceed the acceptable daily intake (ADI) level in their Accuretic products. This is a global issue, with voluntary recalls happening in other countries, including in Australia, Europe, the US, and Canada. Medsafe has issued a safety alert and Pharmac has advised prescribers to stop prescribing Accuretic and to urgently switch patients currently taking Accuretic to alternative options.

In New Zealand, there are 35,077 people taking Accuretic: 23,825 patients taking Accuretic (20mg + 12.5mg) and 11,252 taking Accuretic (10mg + 12.5mg). Almost all practices in New Zealand (98 per cent) have at least one enrolled patient taking Accuretic.

N-Nitroso-quinapril is a nitrosamine. Nitrosamines can be found in water and foods, including cured and grilled meats, dairy products and vegetables and are classified as probable human carcinogens (substances that could cause cancer). Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels over long periods of time.

For this reason, Pharmac is advising prescribers to:

- **Not start any new patients on Accuretic**.
- **Urgently switch patients currently taking Accuretic to an alternative ACE inhibitor/angiotensin II receptor blocker (ACEi/ARB) or an alternative blood pressure-lowering medicine**.

Current supplies of Accuretic will begin to be disrupted from August 2022, therefore this switch is required as soon as possible. Once supplies of Accuretic are exhausted, it is unlikely to be available again for at least 12 months. People currently taking Accuretic must continue taking it until an alternative has been prescribed, as the risk of suddenly stopping medication for blood pressure is higher than the potential risk presented by the impurity.

## Switching advice

A straight switch from Accuretic to another combination of quinapril and hydrochlorothiazide is not possible. There is no other quinapril + hydrochlorothiazide (or alternative thiazide or thiazide-like diuretic) combination tablet available in New Zealand. Although the single agent quinapril tablet remains available, and has not been affected by the Accuretic impurity, hydrochlorothiazide is not available here as a single agent to use alongside it.

Therefore, alternative fully funded options to Accuretic include a combination ARB + hydrochlorothiazide, or quinapril (single agent) or another ACEi/ARB used in combination with a different thiazide or thiazide-like diuretic. Current options for switching from Accuretic to other agent(s) include:

- losartan + hydrochlorothiazide – this is the only alternative funded ACEi/ARB + thiazide diuretic combination available
- quinapril (single agent) or another ACEi/ARB, in combination with a thiazide or thiazide-like diuretic such as bendroflumethiazide
- alternative blood-pressure-lowering medicine(s).

Examples of each of these three options are given below.

### 1. Changing patients from Accuretic to losartan + hydrochlorothiazide

This may be the easiest option for the patient as it enables the continuation of treatment with a single tablet. The dose of hydrochlorothiazide in this combination is the same as it is in the Accuretic formulations, however there is only one strength of losartan + hydrochlorothiazide (Arrow – Losartan & hydrochlorothiazide 50mg + 12.5mg). Refer to Table 1, below, for dose equivalence of losartan to quinapril.

Example: for a patient taking once daily Accuretic (either 10mg + 12.5mg or 20mg + 12.5mg), change to Arrow – Losartan & hydrochlorothiazide 50mg + 12.5mg, one tablet once daily. Monitor blood pressure after two to four weeks; the dose may need increasing if blood pressure is elevated beyond baseline after four weeks.

### 2. Changing patients from Accuretic to quinapril (single agent) or another ACEi/ARB in combination with a thiazide or thiazide-like diuretic

This option enables the patient to continue to use quinapril but will require adding an alternative thiazide or thiazide-like diuretic as a separate tablet. This increases the

pill burden for patients and may be problematic for people who are already experiencing polypharmacy. The steps for this change are:

- Prescribe the same dose of quinapril that the patient had in their Accuretic product.
- Using Table 2 (below) as a guide, prescribe an equivalent dose of an alternative thiazide or thiazide-like diuretic.
- It is possible to discontinue an ACEi one day and start another ACEi or ARB the following day. This is also true for changing a thiazide diuretic.

Example: for a patient taking Accuretic (20mg + 12.5mg), change to quinapril 20mg and chlorthalidone 12.5mg.

Tables 1 and 2, below, are approximate dose equivalence guides for ACEi/ARBs and thiazide/thiazide-like diuretics. Doses will need adjustment in some cases, such as for people with renal impairment.

Each patient may respond differently, so it is recommended that they are followed up two to four weeks after changing. Assess blood pressure, creatinine and electrolytes, and ask about any adverse effects such as signs of hypotension, or cough.

**Table 1: Approximate dose equivalence guide for ACE inhibitors and ARBs** (adapted from[1-3])

| Quinapril | Enalapril | Lisinopril | Perindopril | Candesartan | Losartan |
|---|---|---|---|---|---|
| 10mg | 5–10mg | 10mg | 2–4mg | 8mg | 50mg |
| 20–40mg | 20mg | 20–40mg | 8mg | 16mg | 50–100mg |

Note that clinical trials show variations in approximate equivalent dosages for ACEi/ARBs.

Only funded options are included in this table.

**Table 2: Approximate dose equivalence guide for thiazide and thiazide-like diuretics** (adapted from[4])

| Hydrochlorothiazide | Bendroflumethiazide | Chlorthalidone | Indapamide |
|---|---|---|---|
| 12.5mg | 2.5mg | 12.5mg | 2.5mg |

Note that clinical trials show variations in approximate equivalent dosages for thiazide diuretics. Lower doses may be necessary in elderly people – refer to NZ Formulary.

3. **Transitioning to a single blood-pressure-lowering medicine or adding an alternative blood-pressure-lowering medicine**

While most patients' transition off Accuretic will be covered by the first two options, there may be some who would benefit from, or prefer to:

- Use an alternative blood-pressure-lowering medicine – calcium channel blockers are also considered a first-line option for hypertension.[5] They could be used as a single agent or added to quinapril (or an alternative ACEi/ARB). The ACCOMPLISH trial found that the combination of an ACEi/ARB with a dihydropyridine calcium channel blocker eg, amlodipine or felodipine, was more effective at reducing cardiovascular events in patients with a high CVD risk, compared with an ACEi/ARB-thiazide diuretic combination.[6]
- Transition to quinapril alone – this may be a possible option for older adults or for those with very well-controlled hypertension.

See the 2018 "Cardiovascular Disease Risk Assessment and Management for Primary Care" guidelines for advice about managing hypertension.

## Patient considerations

When changing from Accuretic to an ACEi or ARB:

- Choose once-a-day treatment wherever possible – simpler treatment regimens improve adherence.
- Where appropriate (see table below) consider an ARB because there is less risk of adverse effects, particularly the dry irritating cough associated with ACE inhibitors.[7]

### ACE inhibitor or ARB?

| Table 3: Guide for choosing between an ACEi and ARB[1] | |
|---|---|
| *Conditions where **either** an ACEi or an ARB are appropriate as a first-line choice:* | *Conditions where an ACEi is the first-line choice:* |
| Hypertension, including people with type 2 diabetes | Heart failure<br>(The combination of sacubitril + valsartan can be considered first-line for heart failure) |
| Chronic kidney disease | Following a myocardial infarction |
| Diabetic nephropathy* | |
| *Unapproved indication for ARB | |

Some patients may be concerned about possible increased cancer risk from nitrosamines in the Accuretic they've been taking long-term. Some key points to provide to patients when discussing the required transition off Accuretic include:

- That most people have a low-level exposure to nitrosamines in the food and water they consume.
- Although a potential excess lifetime cancer risk from N-nitroso-quinapril may exist, it is low based on currently available data.
- There is no immediate risk to patients who have been taking this medication, based on the available data.

Other considerations include:

- The risks of suddenly stopping medication for blood pressure is higher than the potential risk presented by the impurity.
- Patients will need follow-up to ensure blood pressure is controlled and any side effects are tolerable.

A resource for patients is available at healthnavigator.org.nz

## Funding of consultation and prescription copayment(s)

Patients making the change from Accuretic to alternative treatment(s) will not have to pay for the initial consultation with their primary-care prescriber, or for the prescription copayment(s) for the first dispensing.

Extra funding is being added to support primary care with this change. This includes:

- a GP payment for the waived patient consultation fee
- a one-off bulk payment to community pharmacies, which will include a prescription copayment for the first dispensing of the alternative medicine(s) and a payment for work in supporting the patient in the transition.

Additionally, Pharmac is exploring the listing of further treatment options.

Check the Pharmac website for the latest information regarding the Accuretic supply issue, including funding arrangements for prescribers and dispensers.

### Acknowledgements

Written by: Dr Noni Richards (BPharm, PhD)

Reviewed by: Dr Sam Whittaker (MBChB FRNZCGP)

## Useful links

Medsafe safety alert for Accuretic: medsafe.govt.nz/safety/Alerts/Accuretic-nitrosamines.asp

Pharmac advice about Accuretic: https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/accuretic/

NZ Formulary diuretic dosing: https://nzf.org.nz/nzf_998?searchterm=thiazides%20and%20related%20diuretics

*Cardiovascular Disease Risk Assessment and Management for Primary Care* guidelines for advice about managing hypertension: health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care

Health Navigator Accuretic patient resource: https://pharmac.govt.nz/assets/2022-June-30-Health-Navigator-Brochure-Accuretic.pdf

## References


1 bpacnz. Prescribing ACE inhibitors: time to reconsider old habits. *BPJ* Published Online First: March 2021. https://bpac.org.nz

2 Coca A, Kreutz R, Manolis AJ, et al. A practical approach to switch from a multiple pill therapeutic strategy to a polypill-based strategy for cardiovascular prevention in patients with hypertension. *J Hypertens* 2020;38:1890–8. doi:10.1097/HJH.0000000000002464

3 London New Drugs Group. ACE Inhibitors and Angiotensin II Receptor-Antagonists for hypertension. *APC/DTC Briefing Document* 2008.

4 Jentzer JC, DeWald TA, Hernandez AF. Combination of Loop Diuretics with Thiazide-Type Diuretics in Heart Failure. *J Am Coll Cardiol* 2010;56:1527–34. doi:10.1016/j.jacc.2010.06.034

5 Ministry of Health. *Cardiovascular Disease Risk Assessment and Management for Primary Care* 2018. Wellington. Ministry of Health.

6 Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med* 2008;359:2417–28. doi:10.1056/NEJMoa0806182

7 Messerli FH, Bangalore S, Bavishi C, et al. Angiotensin-Converting Enzyme Inhibitors in Hypertension. *J Am Coll Cardiol* 2018;71:1474–82. doi:10.1016/j.jacc.2018.01.058


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