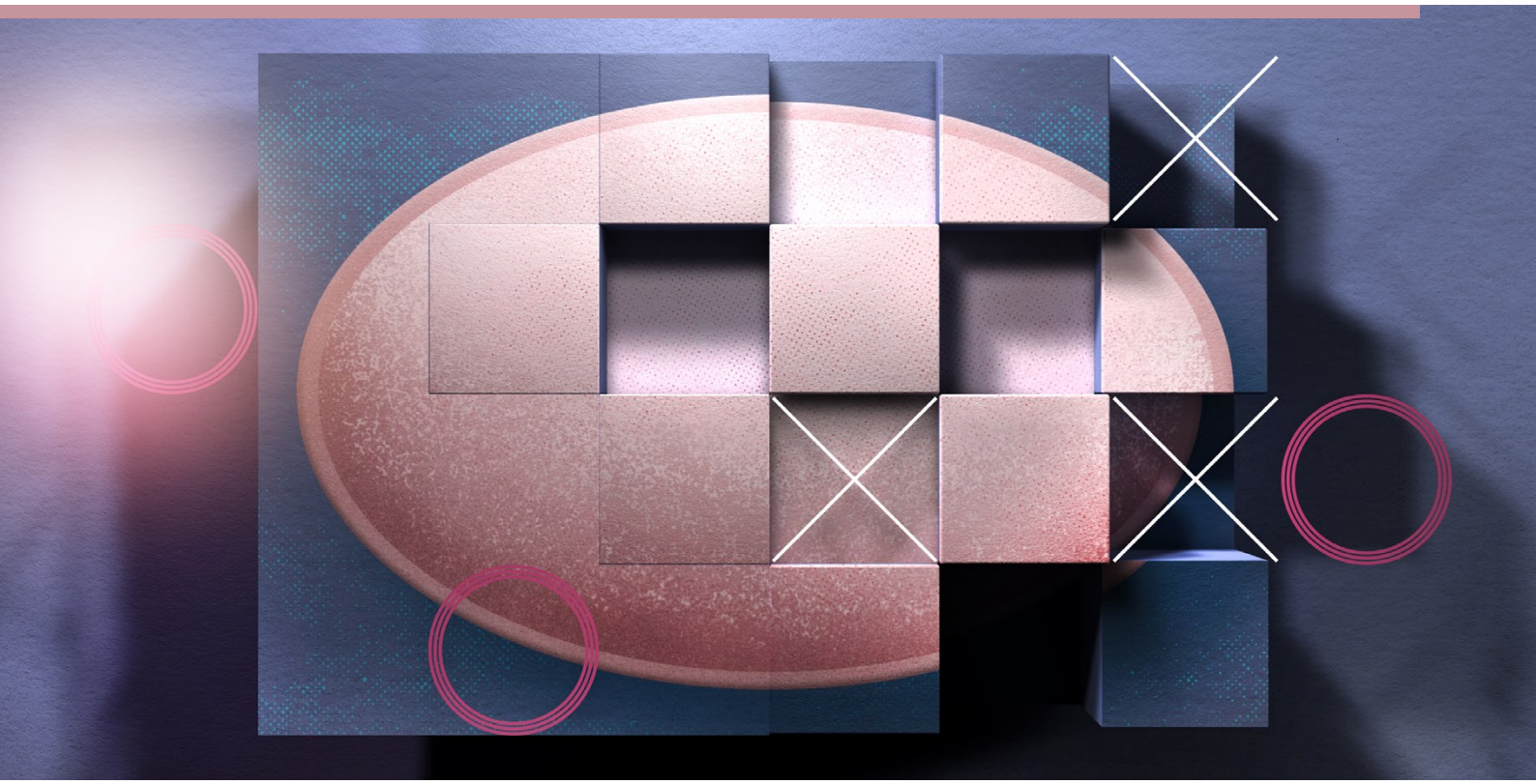


News Update: **cilazapril with hydrochlorothiazide will no longer be available in New Zealand**

Patients currently prescribed cilazapril + hydrochlorothiazide combination tablets will need to transition to a different combination medicine or antihypertensive regimen.

Cilazapril with hydrochlorothiazide is a fixed-dose combination medicine (cilazapril 5mg + hydrochlorothiazide 12.5 mg) for the treatment of patients with hypertension when dual antihypertensive treatment is indicated.[1] Apotex, the supplier of Apo-Cilazapril/Hydrochlorothiazide, has announced that it will no longer be able to supply this medicine in New Zealand.[2] Apo-Cilazapril/Hydrochlorothiazide is the only registered brand of cilazapril with hydrochlorothiazide in New Zealand, therefore this decision will mean that:

- **From 1 March, 2020:** cilazapril with hydrochlorothiazide will no longer be available funded for patients that have never been prescribed this medicine before
  - Prescribers should ensure no new patients are started on this medicine from 1 March, 2020
  - Prescribers will need to endorse* any prescriptions for patients who were taking this medicine prior to 1 March, 2020 and should begin transitioning them to alternative treatments
- **From July, 2020:** current cilazapril with hydrochlorothiazide stocks are anticipated to run out
  - Patients still receiving this combination product after 1 March, 2020 will need to have switched to an alternative regimen by July, 2020

* Pharmacists may annotate a prescription of cilazapril with hydrochlorothiazide as endorsed if a record exists of prior dispensing, if required.

Deciding which antihypertensive regimen to switch to

Patients with hypertension currently taking cilazapril with hydrochlorothiazide will need to transition to an alternative antihypertensive regimen; the decision on the replacement regimen should be individualised. Most patients are likely to prefer to continue using another fixed-dose combination because they have established a familiar dosing routine, and it is likely to have a comparable clinical effect. However, other options include transitioning to two separate antihypertensives, or in rare cases, de-escalating treatment to use of a single antihypertensive.

Transitioning to another fixed-dose combination

As of February 2020, there are two fully funded fixed-dose combination antihypertensives available in New Zealand which are suitable alternatives to cilazapril with hydrochlorothiazide (Table 1).[1] Both also include hydrochlorothiazide,* combined with either an ACE inhibitor (quinapril) or an angiotensin II receptor blocker (ARB; losartan). When transitioning a patient from one fixed-dose combination to another, it is recommended that their blood pressure is checked one month after switching, and then at least once every three to six months after blood pressure targets have been achieved, depending on the patients characteristics and level of cardiovascular disease (CVD) risk.[3]

* See: "Consider the potential increased risk of non-melanoma skin cancers when prescribing hydrochlorothiazide-containing medicines"

Transitioning to two separate antihypertensive medicines

Although prescribing fixed-dose antihypertensive combinations is a valuable strategy to promote medicine adherence, some patients may be satisfied with transitioning to two separate medicines as it allows for a specific choice and customised dosing of the antihypertensives used.

ACE inhibitors/ARBs, calcium channel blockers and thiazide (and thiazide-like) diuretics are all first line antihypertensives with a comparable blood pressure lowering effect.[3] The choice of antihypertensive depends on patient characteristics, co-morbidities, age, tolerance, concomitant medicine use and patient preference. Beta-blockers should only be prescribed as an add-on for resistant hypertension despite use of the three first line medicines, or if there is a specific indication, e.g. atrial fibrillation.[3]

For further information on antihypertensive medicine options, visit the NZ formulary (NZF) at: **https://nzf.org.nz/nzf_1168**

Cilazapril will still be available, but an alternative ACE inhibitor should be considered

The decision to stop supplying cilazapril with hydrochlorothiazide does not apply to cilazapril tablets alone, and supplies of cilazapril have been secured until 2022. However, New Zealand is one of the few countries where cilazapril is used frequently.[4] Given that there is only one manufacturer of the active ingredient in cilazapril, any supply issues in the future would significantly impact patients prescribed this medicine. Therefore, if treatment with two separate antihypertensives is preferred, prescribers should consider using an alternative subsidised ACE inhibitor if appropriate, e.g. enalapril, lisinopril, perindopril, quinapril.

For further information on the prescribing and dosing of ACE inhibitors, see: "Prescribing ACE inhibitors: time to reconsider old habits" at **https://bpac.org.nz/2018/ace.aspx**

Consider prescribing an ACE inhibitor with a dihydropyridine calcium channel blocker for patients with a high CVD-risk.

In general, any combination of first-line antihypertensive medicines is likely to be suitable for patients with uncomplicated hypertension (i.e. without co-morbidities). However, results from the ACCOMPLISH trial suggest that the combination of an ACE inhibitor/ARB with a dihydropyridine calcium channel blocker, e.g. amlodipine or felodipine, is superior for reducing cardiovascular events in patients with a high CVD risk, compared with an ACE inhibitor/ARB-thiazide diuretic combination.[5]

Table 1. Fully funded fixed-dose ACE inhibitor-/ARB-thiazide diuretic combinations for the treatment of hypertension.[1]

Fixed-dose combination medicine	Approximate equivalent strength*	Dosing regimen
Quinapril with hydrochlorothiazide (brand name: Accuretic)	20 mg† quinapril with 12.5 mg hydrochlorothiazide	Initially one 10/12.5 mg tablet, once daily, increased to one 20/ 12.5 mg tablet, once daily, if necessary
Losartan with hydrochlorothiazide (brand name: Arrow-Losartan & Hydrochlorothiazide)	50 mg losartan with 12.5 mg hydrochlorothiazide	Initially one 50/12.5 mg tablet, once daily, increased to 2 tablets (i.e. 100/25 mg), once daily, if necessary

* Compared with 5 mg cilazapril/12.5 mg hydrochlorothiazide

† Quinapril with hydrochlorothiazide is also available in a 10 mg (quinapril) with 12.5 mg (hydrochlorothiazide) preparation

Transitioning to a single antihypertensive medicine

Although the majority of patients will require continued use of two antihypertensives, this necessary transition may be an appropriate time to trial switching to a single first-line antihypertensive in some patients, e.g. long-term users of fixed-dose combinations that have applied major lifestyle changes and are consistently achieving blood pressure targets.

Continued use of an ACE inhibitor is a suitable option for many patients, and if this decision is made then an alternative to cilazapril should be considered (as previously described). Patients should have their blood pressure and renal function checked one to three months following the switch to a single antihypertensive to evaluate whether they should continue at their current dose, require a dose adjustment, or need to transition back to use of two antihypertensives.[3]

Consider the potential increased risk of non-melanoma skin cancers when prescribing hydrochlorothiazide-containing medicines

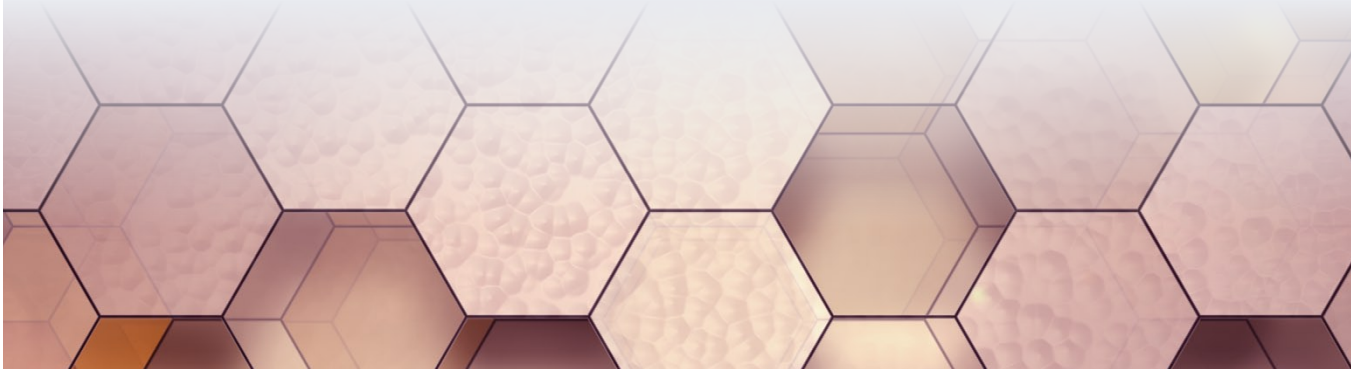
Two Danish case-control studies have reported that hydrochlorothiazide increases the risk of non-melanoma skin cancer, specifically squamous cell carcinoma (SCC), SCC of the lip and basal cell carcinoma (BCC).[6, 7] Although the mechanism is unknown, this association may be due to the photosensitising effect of hydrochlorothiazide. In contrast, a series of Taiwanese case-control studies did not demonstrate an association between hydrochlorothiazide use and the risk of lip cancer, non-lip non-melanoma skin cancer and melanoma.[8] These conflicting findings may be explained by differences in the study populations, i.e. different skin tones and therefore different susceptibility to skin cancer, the dose of hydrochlorothiazide used and cultural practices relating to sun exposure.

While further studies are needed to investigate the association between hydrochlorothiazide and the risk of non-melanoma skin cancers, it is recommended that this potential risk is discussed when deciding on an antihypertensive regimen.[9] If a hydrochlorothiazide-containing medicine is selected, patients should be made aware of, and consistently adhere to, SunSmart practices and perform regular self-checks of their skin for any suspicious looking lesions.[9] For patients who have experienced previous non-melanoma skin cancer, the risks and benefits of hydrochlorothiazide treatment should be thoroughly discussed, taking into consideration other treatment options.[9]

There is currently insufficient evidence to determine if the increased risk of non-melanoma skin cancer is a thiazide class effect.

If an alternative thiazide (or thiazide-like) diuretic is preferred, then indapamide, chlortalidone or bendroflumethiazide are potential options. Indapamide and chlortalidone have the strongest evidence of effectiveness, and the 2019 NICE guidelines state that indapamide is preferred if a decision is made to switch diuretics.[10] For patients where chlortalidone is selected, closer monitoring of serum electrolytes may be warranted as a US observational study reported an increased risk of electrolyte disturbances with chlortalidone compared with hydrochlorothiazide.[11] However, further investigation is required as the dose of hydrochlorothiazide used in this study was 25 mg (twice the amount contained in currently available fixed-dose combinations in New Zealand) and the cohort was restricted to patients aged less than 70 years.[11]

For further information, see "Hydrochlorothiazide: risk of non-melanoma skin cancer" at: **https://www.medsafe.govt.nz/safety/Alerts/Hydrochlorothiazide.asp**



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