Medicines Adverse Reactions Committee

Meeting date	11/09/2025	Agenda item	3.2.2
Title	Angiotensin Converting Enzyme inhibitors and Angiotensin-II receptor blockers and the risk of intestinal angioedema		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
ACE inhibitors		
Lisinopril	Lisinopril Teva*	Teva Pharma
Captopril	Capoten	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
	DP-Captopril*	Douglas Pharmaceuticals Limited
Enalapril	Renitec	Organon (New Zealand) Ltd
	Acetec*	Viatris
Perindopril	Coversyl*	Sevier Laboratories NZ Ltd
Quinapril	Arrow-Quinapril*	Teva Pharma
Ramipril	Tryzan*	Viatris
Combination products	Trinomia (ramipril+aspirin+atorvastatin)	Te Arai BioFarma
ARB		
Candesartan	Candestar*	Viatris
Irbesartan	Irbesartan	Medsurge Pharma Limited
Losartan	Losartan Actavis*	Teva Pharma
Combination products	Entresto (sacubitril+valsartan)*	Novartis
	Arrow-Losartan potassium & hydrochlorothiazide (losartan+hydrochlorothiazide)*	Teva Pharma
	Apo-Candesartan HCTZ tablet (candesartan+ hydrochlorothiazide)*	Arrotex Pharmaceuticals

PHARMAC funding	Marked with *asterisks above.
Previous MARC meetings	Not discussed.
International action	EMA – requested class warning for ARB
Prescriber Update	Reminder: ACE inhibitor-induced angioedema can be fatal (June 2023) Vildagliptin and ACE inhibitors – increased risk of angioedema (March 2021)
Classification	Prescription medicine
Advice sought	**The Committee is asked to advise whether:**

	• For ACE inhibitors
	  ○ If the data sheets should have a consistent warning on intestinal angioedema in section 4.4?
	  ○ If the data sheets should have intestinal angioedema as an adverse reaction (in section 4.8)?
	• For ARB: if there is sufficient evidence of a class effect for ARB and intestinal angioedema?
	  ○ If yes, should the remaining ARB data sheets be updated with a consistent warning on intestinal angioedema in section 4.4?
	  ○ If yes, should the remaining ARB data sheets be updated with intestinal angioedema as an adverse reaction (in section 4.8)?
	  ○ Whether the Entresto (sacubitril + valsartan) data sheet should be updated with intestinal angioedema?
	• Further communication is required other than in MARC's remarks?

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1 PURPOSE

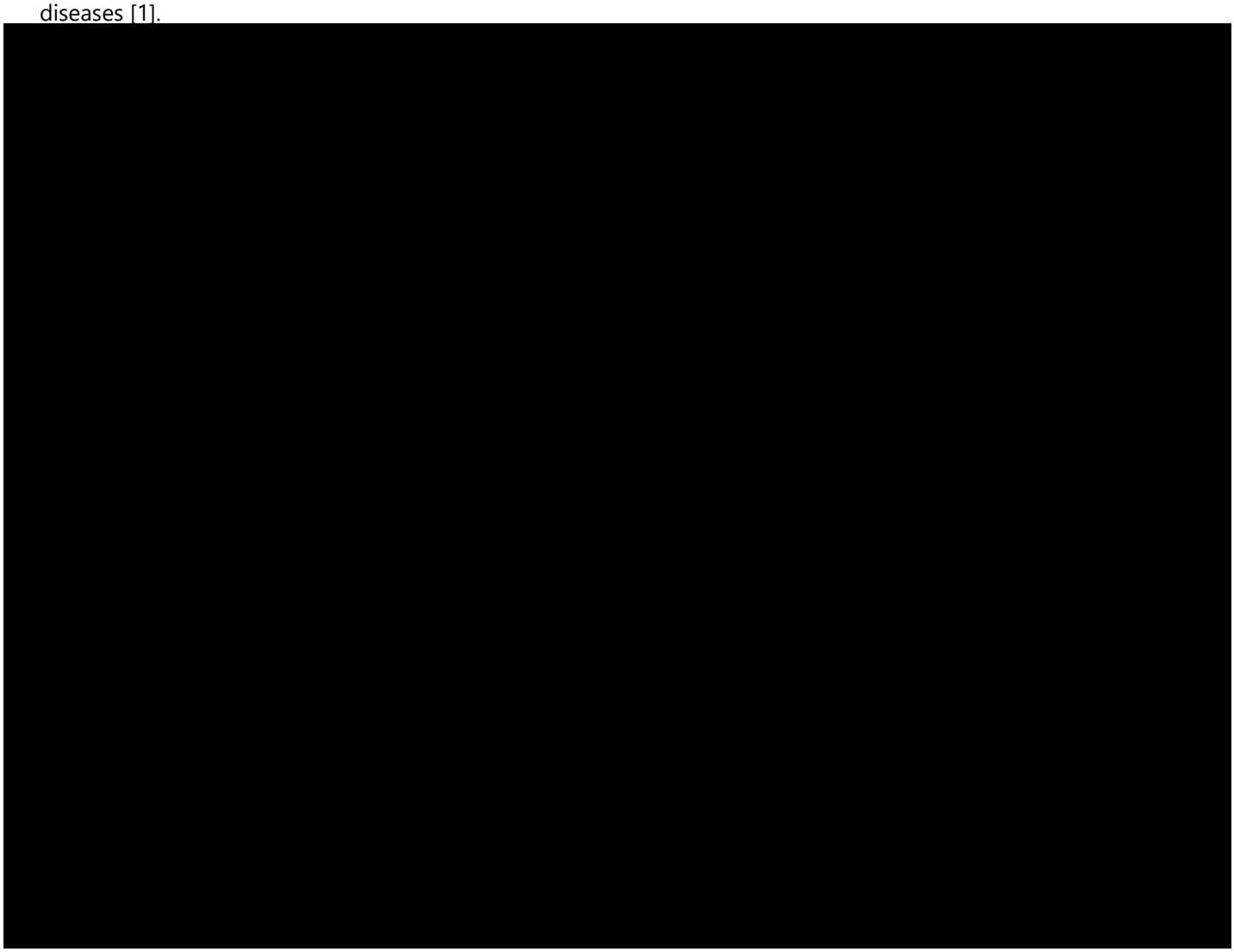
In 2024, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA's PRAC) requested updates to the product information of angiotensin receptor II blockers (ARB) to include a class warning on the risk of intestinal angioedema.

There is variable information in the New Zealand data sheets for Angiotensin Converting Enzyme inhibitors (ACEi) and ARB and the risk of intestinal angioedema. This paper considers the risk of intestinal angioedema with ACEi and ARB and whether regulatory action is required.

2 BACKGROUND

2.1 Renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is a regulator of blood volume, electrolyte balance, and systemic vascular resistance. The RAAS involves multiple organ systems with key proteins and enzymes (Figure 1). Overactivation of RAAS has been implicated in the pathogenesis of various cardiovascular and renal diseases [1].



Renin is produced in the juxtaglomerular cells within the afferent arterioles of the kidney. Renin is released into the circulation through four main triggers: (1) changes in renal perfusion, (2) delivery of sodium and chloride, (3) increased beta-sympathetic flow acting through beta-1 adrenergic receptors and (4) negative feedback from humoral factors like angiotensin I, potassium and atrial natriuretic peptide [1].

Renin cleaves angiotensinogen leading to the formation of angiotensin I. Angiotensin I does not have any known biological activity [1].

Angiotensin converting enzyme (ACE) is expressed on plasma membranes of vascular endothelial cells, primarily in the pulmonary circulation. ACE converts angiotensin I to angiotensin II [1].

Angiotensin II is the primary mediator of the physiological effects of RAAS, which include:

1. Vasoconstriction by contraction of the vascular smooth muscle in the arterioles
2. Aldosterone secretion from the adrenal cortex
3. Increase of sodium reabsorption
4. Increasing sympathetic outflow from the central nervous system
5. Release of vasopressin from the hypothalamus [1].

Angiotensin II has been implicated in the pathogenesis of hypertension, atherosclerotic disease, heart failure, and kidney disease through these effects, mediated by two types of receptors: type 1 and type 2 [1].

Angiotensin II type 1 receptor is widely distributed in many cell types including the heart, vasculature, kidney, adrenal glands, pituitary and central nervous system. Angiotensin II mediates its physiological effects of vasoconstriction and sodium and water reabsorption through this receptor. In pathogenic states, the activation of the type 1 receptor leads to inflammation, fibrosis, oxidative stress, tissue remodelling, and increased blood pressure. The dysregulation of this receptor is central to the pathophysiology of cardiac and renal diseases [1].

Angiotensin II type 2 receptor is mainly expressed in fetal tissues and expression of this receptor decreases in adulthood. This receptor mediates the opposing and protective effects of angiotensin II. These actions inhibit inflammation, fibrosis, and central sympathetic outflow and cause vasodilation. Stimulation of type 2 receptor by angiotensin II leads to vasodilation and natriuresis, opposite to the vasoconstriction and anti-natriuresis caused by angiotensin II via receptor type 1 [1].

2.2 Pharmacodynamics and indications of medicines acting on the RAAS

2.2.1 Angiotensin converting enzyme inhibitors

Medicines that inhibit ACE and therefore the formation of angiotensin II are called ACE inhibitors (ACEi). ACEi are generally indicated for the management of hypertension, and some are approved for heart failure, diabetic nephropathy and the prevention of cardiovascular events [2].

Approved ACEi include lisinopril, captopril, enalapril, perindopril, quinapril and ramipril and a fixed dose combination product containing ramipril, atorvastatin and aspirin [2].

ACE is also responsible for the breakdown of bradykinin, a mediator of vasodilation. ACEi are known to increase bradykinin levels leading to serious events such as angioedema [3]. Angioedema caused by ACEi can occur at any time, including patients who have been taking ACEi for years. Although rare, angioedema can be life-threatening with approximately 20% of ACEi-induced angioedema cases being life-threatening and affecting the upper respiratory tract and larynx [4].

2.2.2 Angiotensin receptor blockers

ARB selectively inhibit the binding of angiotensin II to the angiotensin II type 1 receptor. This leads to vasodilation, reduced aldosterone secretion and reduction in blood pressure [5]. See also Figure 1 above.

The ARB available in New Zealand include candesartan, irbesartan and losartan. There are also fixed dose combination products with hydrochlorothiazide.

ARB may be used as an alternative to ACEi for the management of hypertension. Some ARB are also approved for heart failure and diabetic nephropathy.

ARB are not expected to elevate bradykinin levels, however post-market reports have shown that angioedema can occur, although rarer compared to ACEi [5, 6]. A proposed explanation for ARB mediated angioedema is through the inhibition of angiotensin II type 1 receptor, which in turn increases angiotensin II levels. This increase in angiotensin II may then activate the less-understood AT2 receptor, which can generate bradykinin and lead to angioedema [7].

2.2.3 Neprilysin inhibitors

Neprilysin is an enzyme that degrades the vasoactive substances bradykinin, natriuretic peptides and angiotensin II. Neprilysin inhibitors prevent the breakdown of these substances [8].

Neprilysin inhibitors increase levels of natriuretic peptides resulting in increased diuresis, natriuresis and vasodilation. This has favourable effects on the pathogenesis of heart failure [8].

Neprilysin inhibitors are combined with an ARB to block the effects of excess angiotensin II [8].

The current approved angiotensin receptor-neprilysin inhibitor, sacubitril + valsartan (Entresto) is indicated for chronic heart failure (NYHA Class II-IV) [8].

2.3 Angioedema and intestinal angioedema

2.3.1 Angioedema

Angioedema is a localised subcutaneous (or submucosal) swelling, which results from extravasation of fluid into interstitial tissues. Areas with loose connective tissues are affected such as the face, lips, mouth, throat, extremities, genitalia and bowel [9].

Angioedema may occur in isolation, accompanied by urticaria or as a component of anaphylaxis [9].

There are three types of angioedema and are classified depending on the underlying mechanism.

- Cell mediated angioedema results from histamine release from mast-cells and is associated with urticaria and/or pruritic in most cases. Other signs and symptoms include flushing, bronchospasm, throat tightness and hypotension.
- Bradykinin-induced angioedema is not associated with pruritis, urticaria or other symptoms of mast-cell activation. Bradykinin-induced angioedema has somewhat a more prolonged time course, usually developing over 24 to 36 hours and resolves within 2 to 4 days.
- Aetiology of unknown mechanism [9].

2.3.2 Bradykinin-mediated angioedema

Overproduction of bradykinin or the inhibition of its breakdown can result in angioedema. Bradykinin plays an important role in inflammation and causes vasodilation and increased vascular permeability. This increased blood flow causes the redness and warmth components of the inflammation process [10].

2.3.3 Intestinal angioedema

Patients with intestinal angioedema can present with non-specific symptoms such as colicky abdominal pain, sometimes accompanied by nausea, vomiting, and/or diarrhoea. Intestinal angioedema can often be visualised by abdominal computed tomography (CT) scan or ultrasound [9] .

Intestinal angioedema is a challenging diagnosis since it is a lesser known entity compared to angioedema of the face, tongue, genitals, extremities, or upper airways. In addition, a diagnosis of intestinal angioedema can be missed as other conditions can also present similarly such as bowel ischemia, intramural haemorrhage, vasculitis, inflammatory bowel disease, lymphoproliferative disease, radiation enteritis, nephrotic syndrome with hypoproteinaemia, infectious enteritis, and graft versus host disease [11].

Classically, bradykinin-mediated angioedema is located in the pharynx, extremities, or face. However, the bowel wall may be involved concomitantly in up to 75% of cases. Rarely, angioedema of the intestines may be the only site affected [11].

Intestinal angioedema can be well managed if diagnosed early. Due to the debilitating nature of this condition, and the risk of complications from misdiagnosis (such as surgery or invasive procedures) there is need for a low threshold for suspicion among healthcare professionals. Healthcare professionals should be cognisant of medicines that can induce intestinal angioedema particularly ACEi, in order to immediately discontinue use of the medicine [11].

2.4 Data sheets

2.4.1 New Zealand

Tables 1 and 2 show the New Zealand data sheet wording on intestinal angioedema, if any, for ACEi and ARB respectively. The data sheet of the currently funded brand was reviewed if the innovator product was not available.

Table 1: Review of ACEi data sheets and information on intestinal angioedema

Lisinopril
Lisinopril (Teva) Section 4.8 In very rare cases, intestinal angioedema has been reported.
Captopril
Capoten Section 4.4 Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain. Section 4.8 Less common reactions – intestinal angioedema
Enalapril
Renitec Section 4.8 In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.
Perindopril
Coversyl Section 4.4 Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.
Quinapril
Arrow-Quinapril Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there has been no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Ramipril
Tryzan Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor. Section 4.8 Small bowel angioedema
Combination products
Trinomia (ramipril+aspirin+atorvastatin) Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting). Section 4.8 Small bowel angioedema – with an uncommon ADR frequency

Comments:

Overall, there is information on intestinal angioedema in the data sheets for all ACEi, although the level of information and the section it is presented varies. Some data sheets only have a warning (in section 4.4) while others (eg, lisinopril and enalapril) only list intestinal angioedema as an ADR in section 4.8.

The data sheets for captopril, perindopril and quinapril provide an informative warning in section 4.4. They cover the following concepts:

1. Intestinal angioedema has been reported with ACEi.
2. The symptoms and signs of intestinal angioedema.
3. Intestinal angioedema was diagnosed by CT scan or ultrasound, or at surgery.
4. Symptoms resolved after stopping the ACEi.
5. Intestinal angioedema should be included in the differential diagnosis of patients on ACEi presenting with abdominal pain.

Table 2: Review of ARB data sheets and information on intestinal angioedema

Candesartan
Candestar Section 4.4 Intestinal angioedema Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including candesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, candesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8 Intestinal angioedema, as post-market ADR with no frequency.
Irbesartan
Irbesartan Medicianz No information.
Losartan

Losartan Actavis Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8 Undesirable effects). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8 – intestinal angioedema with ADR frequency 'rare'.
Combination products
Entresto (sacubitril+valsartan) No information.
Arrow-Losartan potassium & hydrochlorothiazide Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8 Undesirable effects). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8 Intestinal angioedema – with an ADR frequency 'rare'.
Apo-Candesartan HCTZ (candesartan+hydrochlorothiazide) No information.

Comments:

The warnings in section 4.4 for Candestar, Losartan Actavis and Arrow-Losartan potassium & hydrochlorothiazide follow the EMA's requested wording. They contain the following concepts:

1. Intestinal angioedema has been reported with this class.
2. Outline the symptoms presented and that they resolved after discontinuation.
3. If intestinal angioedema is diagnosed, the ARB should be stopped and appropriate measures taken.

2.4.2 International

Tables 3 and 4 compares the prescribing information in the UK, Ireland and Australia for ACEi and ARB respectively.

Table 3: International product information for ACEi and intestinal angioedema

	UK	Irish	Australian
Lisinopril	Zestril Section 4.8: Intestinal angioedema – very rare		
Captopril	Captopril Section 4.4 Intestinal angioedema has also been reported very rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8 undesirable effects). Section 4.8: Intestinal angioedema as a rare ADR	No products	Captopril Section 4.4 Intestinal angioedema has also been reported very rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8 undesirable effects). Section 4.8: Intestinal angioedema as a less common ADR
Enalapril	Innovace Section 4.8: Intestinal angioedema as a very rare ADR.	Innovace Section 4.8: Intestinal angioedema as a very rare ADR.	Renitec Section 4.8: Intestinal angioedema has been reported in very rare cases
Perindopril	Coversyl Section 4.4 Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and	Pendrex Section 4.4 Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and	Coversyl Section 4.4 Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be

	symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.	symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.	included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.
Quinapril	No products	Accupro Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain. Section 4.8: Small bowel angioedema as a very rare ADR	No products
Ramipril	Tritace Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors including TRITACE (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting). Section 4.8: Small bowel angioedema – uncommon ADR	Tritace Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors including TRITACE (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting). Section 4.8: Small bowel angioedema – uncommon ADR	Tryzan Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor. Section 4.8: Small bowel angioedema
Ramipril+ aspirin+ atorvastatin	No product	Trinomia Section 4.4 Intestinal angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting). Section 4.8 Small bowel angioedema – uncommon ADR	No product

Table 4: International product information for ARB and intestinal angioedema

	UK	Irish	Australian
Candesartan	Candesartan Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including candesartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, candesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: Intestinal angioedema as a very rare ADR	Candesartan Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including candesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, candesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: Intestinal angioedema as a very rare ADR.	Atacand No information
Irbesartan	Irbesartan Mylan Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including irbesartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, irbesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: Intestinal angioedema as rare	Karvea Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including Karvea (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Karvea should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: Intestinal angioedema as rare	Karvea Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including Karvea (see Section 4.8 Adverse effects). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Karvea should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: Rare cases of intestinal angioedema.
Losartan	Losartan Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of	Cozaar Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of	Cozaar Section 4.8: Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists including few cases with losartan.

	angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a rare ADR.	angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a rare ADR.	
Losartan+ HCZT	Cozaar Comp Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a rare ADR.	Cozaar Comp Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a rare ADR.	No products.
Candesartan + HCZT	No products	Catasart Plus Section 4.4 Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including candesartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, candesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a very rare ADR.	Atacand Plus No information.
Entresto	Entresto Section 4.4	Entresto Section 4.4	Entresto No information.

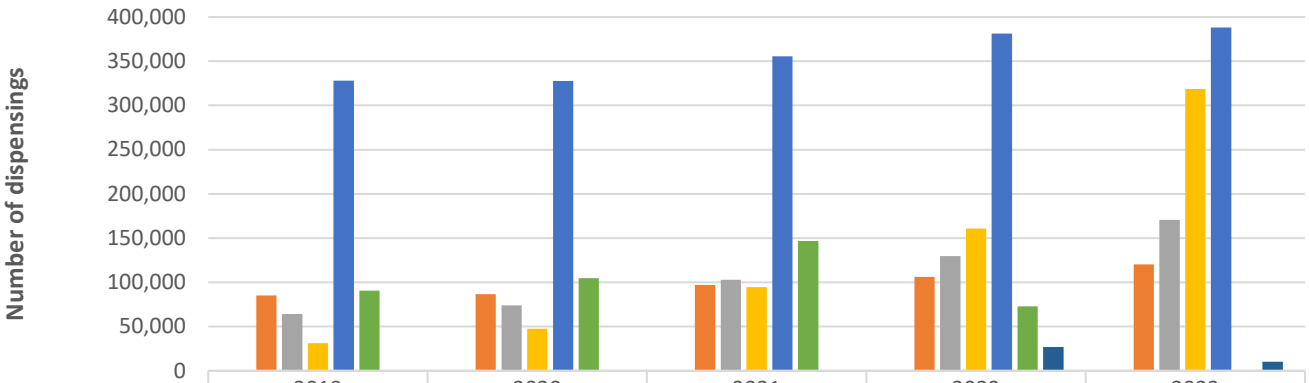
	Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, sacubitril/valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a very rare ADR.	Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, sacubitril/valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred. Section 4.8: intestinal angioedema as a very rare ADR.	

2.5 Usage

Figures 2 and 3 show ACEi and ARB usage by number of (a) dispensings and (b) number of people who received a dispensing from 2019 to 2023.

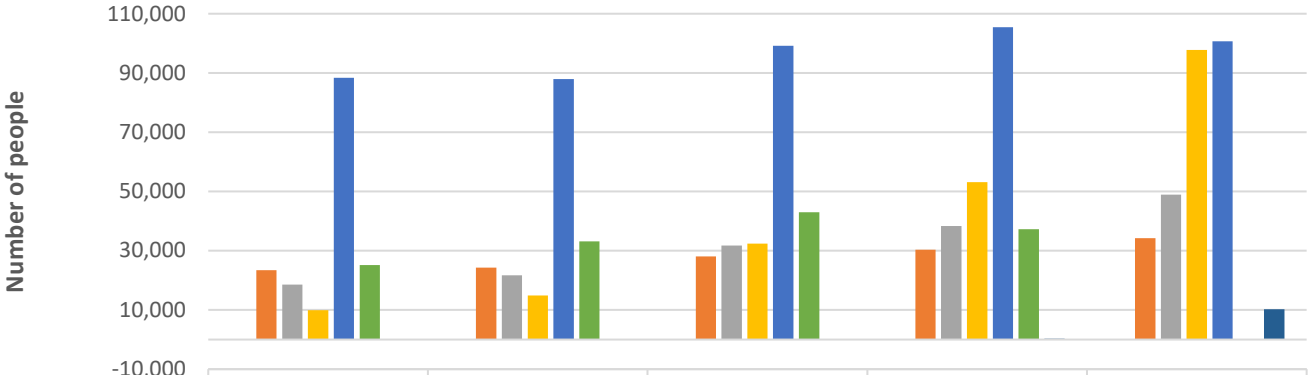
Figure 2: Usage of ACEi in New Zealand from 2019 to 2023

(a) Number of initial dispensings[a]



	2019	2020	2021	2022	2023
Captopril	413	440	242	228	237
Enalapril	85,070	86,654	97,055	106,098	120,339
Lisinopril	64,345	73,918	102,898	129,569	170,446
Perinopril	31,423	47,566	94,441	160,967	318,712
Quinapril	327,858	327,665	355,605	381,015	388,150
Quinapril + HCZT	90,655	104,757	146,799	72,920	55
Ramipril				27,082	10,211

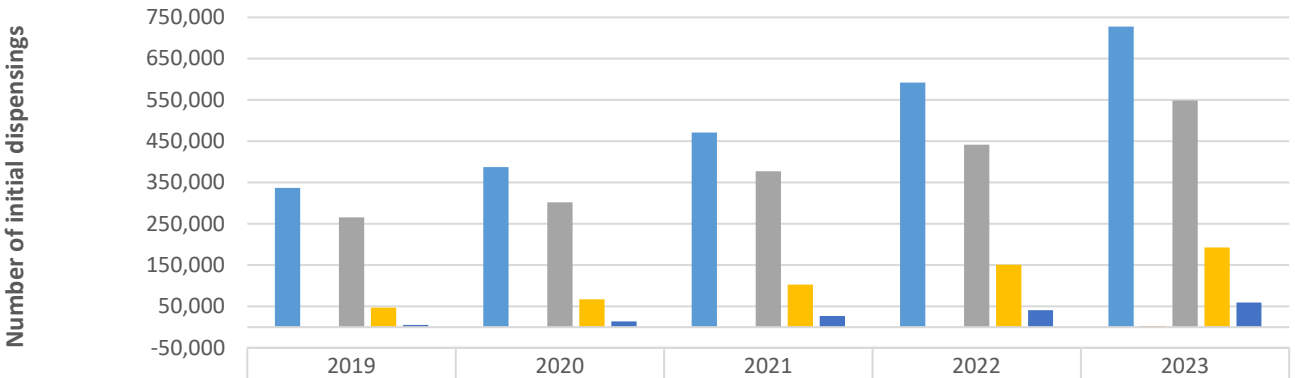
(b) Number of people[b]



	2019	2020	2021	2022	2023
Captopril	128	124	82	76	79
Enalapril	23,410	24,245	28,011	30,293	34,219
Lisinopril	18,574	21,680	31,792	38,340	48,892
Perinopril	9,874	14,873	32,344	53,157	97,783
Quinapril	88,346	87,894	99,199	105,444	100,727
Quinapril + HCZT	25,124	33,120	42,983	37,201	0
Ramipril				331	10,211

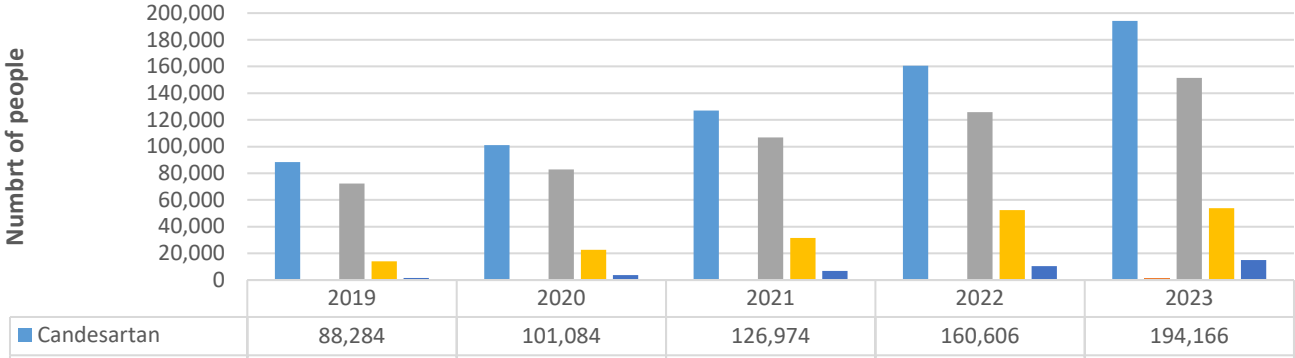
Figure 3: Usage of ARB in New Zealand from 2019 to 2023

(a) Number of initial dispensing[a]



	2019	2020	2021	2022	2023
Candesartan	337,503	387,396	471,069	592,220	727,728
Candesartan + HCTZ					2,222
Losartan	265,576	302,344	377,088	441,927	548,394
Losartan + HCTZ	47,621	67,475	103,057	151,464	192,702
Sacubitril + valsartan	5,615	14,133	27,173	40,888	59,635

(b) Number of people[b]



	2019	2020	2021	2022	2023
Candesartan	88,284	101,084	126,974	160,606	194,166
Candesartan + HCTZ					1,434
Losartan	72,311	82,797	106,876	125,807	151,510
Losartan + HCTZ	14,118	22,707	31,431	52,476	53,877
Sacubitril + valsartan	1,663	3,779	6,900	10,342	14,970

Notes:

a. Dispensings: Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.
b. People: Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Te Whatu Ora Health New Zealand Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 30 July 2025).

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature review was conducted for ACEi and ARB and the risk of intestinal angioedema. Key words used in the search were 'angiotensin converting enzyme inhibitor', angiotensin receptor blocker/antagonist' and

medicines belonging to ACEi and ARB plus 'intestinal angioedema' and 'visceral angioedema'. Case reports and series were identified. These are summarised in Tables 5 and 6.

3.1.1 Case reports of intestinal angioedema with ACEi

Table 5: Literature case reports of intestinal angioedema with ACEi

Author (year published), [ref#]	Age in years and sex	Suspect medicine (indication)	Narrative	Time to onset	Diagnosis	Management	Re-challenge/de-challenge?
Pedroff (2025), [12]	39, female	Lisinopril, losartan, telmisartan (hypertension)	Presented with several months of afebrile, non-specific gastrointestinal symptoms including severe abdominal pain, bloating, nausea and diarrhoea. Lisinopril was stopped and abdominal pain resolved within three days. She was then changed to losartan, but her abdominal symptoms reappeared within 12 hours. Losartan was stopped and changed to another ARB, telmisartan where her abdominal pain reappeared. Following cessation of telmisartan and initiating an alternative medicine that did not contain an ACEi or ARB, the person remained symptom free.	UNK	Clinical presentation and CT scan	Medicines withdrawn	Positive de-challenge and positive rechallenge on ARB
Gillion (2019), [13]	41, female	Enalapril (hypertension)	Presented to ED with severe abdominal pain. CT scan showed jejunal wall oedema with ascites. ACEi-induced intestinal angioedema was suspected and enalapril was stopped. Her abdominal pain then resolved.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive de-challenge
Parreira (2020), [14]	32, female	Perindopril (hypertension)	Presented to ED with a 24-hour history of diffuse abdominal pain associated with nausea and frequent bilious vomiting. Her symptoms coincided with when she started on perindopril. Due to severe abdominal pain, resembling an acute abdomen, an emergency diagnostic laparoscopy was performed which only showed free serous intra-abdominal fluid. The fluid was drained and appendectomy was performed. A month later the symptoms reoccurred and ACEi-induced intestinal angioedema was suspected. Perindopril was stopped and symptoms resolved after 48 hours.	1 month	Clinical presentation, recurrence of symptoms during continued treatment with perindopril	Medicine withdrawn	Positive dechallenge
Voore (2015), [15]	43, female	Lisinopril (hypertension)	Presented with abdominal pain, nausea and vomiting for one week with diffusely tender abdomen with hypoactive bowel sounds. She started on lisinopril four weeks prior. Lisinopril was withheld due to persistent vomiting. After five days her symptoms improved. Lisinopril was then resumed, and her abdominal symptoms reappeared within a day.	3 weeks	Clinical presentation and reoccurrence of symptoms when rechallenged	Medicine withdrawn	Positive dechallenge Positive re-challenge

Sravanthi (2020), [16]	44, male	Lisinopril (hypertension)	Presented to ED with severe and throbbing lower abdominal pain, nausea and loose stools for the past two days. A CT scan confirmed angioedema. Lisinopril was stopped and the person improved.	~3 weeks	CT scan	Medicine withdrawn	Positive dechallenge
Weingärtner (2009), [17]	67, female	Ramipril (hypertension)	Two days after starting lisinopril, the person complained of a hoarse, raspy voice and progressive abdominal pain. Laboratory investigations were normal however CT scan showed marked thickening of the proximal jejunum and ascites. Acute gastroenteritis was suspected and the patient was sent home. The next day, she returned with worsening abdominal pain. She then began complaining of progressive hoarseness of her voice and difficulty breathing. Physical exam showed a very large swelling in the oropharynx. ACEi-induced angioedema was suspected and lisinopril was withdrawn. Following this, her respiratory and abdominal symptoms progressively improved.	2 days	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Campbell (2010), [18]	45, female	Enalapril (hypertension)	The person presented to ED with severe abdominal pain, nausea, vomiting and watery diarrhoea for several days. A CT scan showed mild oedema in the small bowel. Shortly after her CT scan, the person developed angioedema of the face and oral pharynx. ACEi-induced angioedema of the oral pharynx and small intestine was diagnosed and enalapril with withdrawn. On follow up visits, the person's abdominal pain had not returned.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Kale (2024), [19]	47, male	Lisinopril (hypertension)	Presented to ED with abdominal pain. CT scan showed oedematous thickened mesenteric oedema. Lisinopril was stopped and symptoms resolved.	4 days	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Wilin (2018), [20]	62, female	Lisinopril	The person presented with nausea and intermittent left middle and upper quadrant abdominal pain. Her CT scan showed segmental small bowel thickening and oedema with ascites. Two days after stopping lisinopril, her symptoms improved.	2 years	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Augenstein (2013) case 1, [21]	Middle aged female	Lisinopril (hypertension)	The person reported severe abdominal pain, cramping, nausea and vomiting. On examination she had considerable periumbilical and right quadrant tenderness. CT scan showed moderate ascites and a segment of oedematous small intestine.	48 hours	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge

			A diagnosis of intestinal angioedema induced by ACEi was made and lisinopril was discontinued and symptoms resolved.				
Augenstein (2013) case 2, [21]	Middle-aged female	Lisinopril (hypertension)	The person was admitted to the gastroenterology service with abdominal pain and diarrhoea. She has been hospitalised twice during a three-month period with the same complaint and endoscopy was performed on both occasions with negative results. CT scan of her most recent admission showed a thickened small intestine. The patient was initially treated for enteritis—vs a differential diagnosis of acute inflammatory bowel disease—with a course of antibiotics for 7 days without complete resolution of her symptoms. Lisinopril was incidentally stopped as she was nil by mouth, but resumed on discharge where she experienced symptoms again. ACEi induced intestinal angioedema was diagnosed and lisinopril was discontinued with resolution of symptoms after 72 hours.	UNK	Clinical presentation, CT scan and positive dechallenge	Medicine withdrawn	Positive dechallenge Positive rechallenge
Niyibizi (2023), [22]	61, female	Lisinopril (hypertension)	The person presented to ED with severe, diffuse episodic abdominal pain. The symptoms started two months prior. She had previously sought medical attention twice with similar symptoms but without resolution. CT scan showed submucosal oedema of the jejunum and engorgement of the mesenteric vessels. ACEi-induced angioedema was diagnosed given the patient's use of lisinopril. Lisinopril was stopped and the following day her symptoms had completely resolved.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Lee (2022), [23]	49, female	Lisinopril (hypertension)	Within the past couple of years, the person experienced gastrointestinal symptoms, including abdominal pain, cramps, diarrhoea and frequent nausea episodes.	UNK	UNK	UNK	UNK
Gabriel (2018), [24]	68, female	Lisinopril	Presented with hypotension and acute kidney injury with a 1 month history of large-volume diarrhoea. On examination, there was left lower quadrant abdominal tenderness and CT scan showed diffuse non-obstructive distention of the small bowel. ACEi-induced visceral angioedema was suspected given other negative findings. Lisinopril was stopped and she remained symptom free for three years until lisinopril was restarted again. Symptoms again resolved once lisinopril was stopped.	1 year 11 months	Clinical presentation and CT scan. Positive rechallenge	Medicine withdrawn	Positive dechallenge Positive rechallenge

Byrne (2000) case 1, [25]	67, female	Fosinopril (hypertension)	Presented to the ED with epigastric pain, nausea and vomiting. This coincided with starting fosinopril 3 days prior. A CT scan showed dilated and thickened loops of small bowel and ascites. Fosinopril was withdrawn and she was subsequently free from abdominal pain.	3 days	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Byrne (2000) case 2, [25]	41, female	Lisinopril (hypertension)	Presented to the ED with a 2-day history of worsening crampy abdominal pain with intermittent nausea and vomiting. The patient had undergone cholecystectomy 1 month before this presentation after experiencing similar abdominal pain. A CT scan revealed marked thickening of the small bowel extending to the distal ileum and some ascites. The person underwent surgery. A diagnosis of ACEi-induced visceral angioedema was suspected and lisinopril was stopped. The patient remained free of symptoms with more than 1 year of follow up.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Marmery (2006), [26]	48, female	Lisinopril (proteinuria)	Presented with a 24 hour history of diarrhoea and vomiting, and similar symptoms two weeks prior which resolved when she stopped all her oral medicines due to intolerance. On examination she had diffuse abdominal tenderness and CT scan showed moderate amount of ascites in the abdomen and marked mucosa and submucosal oedema affecting the duodenum. Lisinopril was stopped and symptoms resolved. Repeat CT after 24 hours showed complete resolution.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge Positive rechallenge
Inayat (2016), [27]	53, female	Lisinopril (hypertension)	Presented with abdominal pain and diarrhoea for the past day. On examination she had significant epigastric tenderness in the right upper quadrant and left lower quadrant. CT scan showed a large amount of free fluid within the abdomen and mucosal oedema throughout the small bowel. ACEi-induced intestinal angioedema was suspected and lisinopril was stopped. The person's symptoms started to improve.	~2 months	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Korniyenko (2011), [28]	57, female	Lisinopril (hypertension)	Presented to ED with severe, dull abdominal pain associated with vomiting and nausea. She started on lisinopril 4 years ago and had episodes of abdominal symptoms. This led to procedures such as a colonoscopy and laparotomy for suspected small bowel obstruction. Her symptoms persisted.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge

			A CT was performed showing diffuse thickening of the duodenal wall, jejunum and areas of the stomach. Ascites was noted around the liver and small intestines. The person was diagnosed with ACEi-induced intestinal angioedema and lisinopril was stopped. Her symptoms resolved completely within 24 hours.				
Oliveira (2015), [29]	46, female	Ramipril (hypertension)	Presented to ED with a one-day crampy abdominal pain, associated with nausea and vomiting. On examination her abdomen was tender and CT scan revelated thickening of a jejunal segment, with submucosa oedema and moderate ascites. Performed push enterostomy and biopsies revealed normal results. She was diagnosed with ACEi-induced intestinal angioedema and ramipril was stopped. Her symptoms resolved completely in 48 hours.	15 days	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Krause (2019), [30]	57, female	Lisinopril (hypertension)	Presented to ED with acute onset of abdominal pain, nausea, vomiting and 7 episodes of watery diarrhoea for 1 day. A CT scan showed wall thickening adjacent fat stranding and mesenteric oedema of the small bowel and small amount of fluid in the upper abdomen and pelvis. Of note, the person had been hospitalised with similar presentations on two other occasions approximately 4 and 9 years ago. Lisinopril was stopped and symptoms resolved within a day suggesting ACEi-induced visceral angioedema.	UNK	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Savino (2017), case 1, [31]	71, female	Lisinopril (hypertension)	Presented with left-sided abdominal pain that was intermittent for the past 9 months. An MRI showed wall thickening and marked oedema of a long segment of the left upper abdominal proximal jejunum. There was also a small volume fluid. A diagnosis of intestinal angioedema was suggested and lisinopril was stopped. A follow up after three days showed no bowel abnormalities, and at two-months her abdominal pain significantly improved.	9 months	Clinical presentation and MRI/CT scan	Medicine withdrawn	Positive dechallenge
Savino (2017), case 2, [31]	41, female	Lisinopril (hypertension)	Presented with an acute onset of abdominal pain. MRI showed a long segment of abnormal distal jejunum in the central and left mid-abdomen. There was also ascites in the area. A	UNK	Clinical presentation and MRI/CT scan	Medicine withdrawn	Positive dechallenge

			diagnosis of ACEi-induced angioedema was made and lisinopril was stopped. Her symptoms improved and a follow up MRI and CT scan on day 5 showed radiographic resolution.				
Savino (2017), case 3, [31]	41, female	Lisinopril (hypertension)	Presented with new abdominal pain after starting lisinopril three days ago. MRI scan showed long segment of circumferentially thickened distal jejunum and proximal ileum in the lower midline abdomen. Lisinopril was discontinued and person's symptoms resolved	3 days	Clinical presentation and MRI	Medicine withdrawn	Positive dechallenge
Huynh (2022), [32]	44, female	Perindopril (hypertension)	Presented to ED with a one day history of severe abdominal pain after starting perindopril a day prior. Her CT scan showed moderate ascites and bowel wall thickening with submucosal oedema about the duodenum and proximal jejunum. ACEi-induced intestinal angioedema a was suspected and perindopril was stopped. She was discharged three days later with complete resolution of symptoms.	1 day	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Pinto (2022), [33]	32, female	Lisinopril (hypertension)	Presented to ED with worsening left upper quadrant pain, nausea, vomiting, diarrhoea and lip swelling for the past 5 days. CT scan showed dilated, thickened small bowel loops with a small amount of free fluid. Lisinopril was discontinued and her symptoms improved.	6 months	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Pirzada (2023), [34]	58, female	Lisinopril (hypertension)	Presented to ED with abdominal pain, nausea and vomiting. She had been experiencing similar recurrent episodes over the last three years which coincided with starting lisinopril around the same time. The most recent CT scan of the abdomen and pelvis revealed thickening of the small bowel wall with oedema along the proximal and mid small bowel along with adjacent fluid and a small amount of ascites. ACEi-induced intestinal angioedema was suspected and lisinopril was stopped. A repeat CT scan the next day showed substantial improvement.	3 years	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Adam (2025), [35]	32, female	Lisinopril (hypertension)	Presented with 2 days of progressively worsening abdominal pain, nausea and vomiting with a 1 year history of episodic abdominal pain, nausea and vomiting. Crohn's previously stable for 5 years. CT scan showed extensive marked small bowel wall thickening and free fluid.	Few weeks	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge

			The person was treated for presumed exacerbation of her Crohn's disease and lisinopril was withheld due to hypotension. Within the next 24 hours her symptoms improved. ACEi-induced intestinal angioedema was suspected and lisinopril was permanently stopped.				

3.1.2 Case reports of intestinal angioedema with ARB

Table 6: Literature case reports of intestinal angioedema with ARB

Author (year published)	Age in years and sex	Suspect medicine (indication)	Narrative	Time to onset	Diagnosis	Management	Re-challenge/de-challenge?
Almeida (2017), [36]	82, female	Losartan (hypertension)	Presented with mid-epigastric pain, emesis and diarrhoea. On examination there was tenderness in the epigastric area. CT scan showed marked thickening of the jejunum. Losartan was stopped and clinical improvement was seen within 72 hours.	~4 months	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Mousa (2016), [37]	51, male	Losartan (hypertension)	Presented with a three year history of intermittent abdominal pain, diarrhoea and non-tender, non-itchy swelling of upper and lower extremities. Each episode lasted for 5-8 weeks prior to resolution. A CT scan of his abdomen showed jejunal segmental thickening suggestive of jejunal enteritis or oedema. Losartan was discontinued and the frequency and severity of the abdominal pain and swelling of the extremities decreased. His CT scans were unremarkable after 3 weeks.	UNK	Clinical presentation and CT scan	Positive dechallenge	Positive dechallenge
Rosas (2023), [38]	81, female	Losartan (hypertension)	This person visited the ED four times with abdominal pain and nausea before losartan was discontinued. It was identified that these symptoms coincided with starting losartan five weeks prior. Within three days of stopping losartan her abdominal pain resolved and she had no recurrence of abdominal pain during follow up visits.	5 weeks	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge
Hanefeld-Fox (2018), [39]	72, male	Sacubitril/valsartan (systolic congestive heart failure)	Presented with vomiting, dysphagia, and epigastric pain. CT scan showed distended small bowel loops and distended stomach, small bowel obstruction and ileus.	Unspecified	Clinical presentation and CT scan	Medicine withdrawn	Positive dechallenge

			The person underwent surgery and follow up CT scan showed slightly dilated small bowel loops in region of upper abdomen devoid of free fluid or free air. Sacubitril/valsartan was discontinued and symptoms improved.				

Comments:

The case narratives and discussion of these case reports highlight the following:

- Many of the patients discussed in the literature underwent invasive procedures before a diagnosis of ACE-inhibitor induced angioedema was made. Swift recognition is necessary to prevent unwarranted procedures, surgical intervention (Campbell et al 2010)
- Occasionally, the diagnosis is made after symptoms return following reinitiation of the ACE inhibitors after hospital discharge. Therefore, a high index of clinical suspicion should be maintained in patients on therapy with ACE inhibitors presenting with gastrointestinal symptoms. (Inayat 2016)
- Even though ARBs seem to be safer, angioedema can recur in up to one-third of patients who switch from an ACE inhibitor to an ARB (Korniyenko 2011)

Interestingly all cases for ACEi above were in females, and majority were middle aged. Lisinopril was the ACEi most commonly reported however this may reflect the wide use of this ACEi.

There were relatively few case reports for ARB and most were for losartan.

3.2 Regulatory review

3.2.1 European Medicines Agency

The EMA's review was specific to ARB and intestinal angioedema. The review included 45 cases identified in the Eudrovigilance database involving: olmesartan, olmesartan/hydrochlorotiazide, olmesartan/amlodipine, candesartan, irbesartan, losartan, valsartan and valsartan/sacubitril [40].

The PRAC concluded based on the established link between intestinal angioedema and other renin-angiotensin system inhibitors, intestinal angioedema could be considered a class effect of ARB [40]. The PRAC recommended that the product information for the ARB be updated (Table 7).

Table 7: EMA PRAC's requested update of the summary of product characteristics for ARB

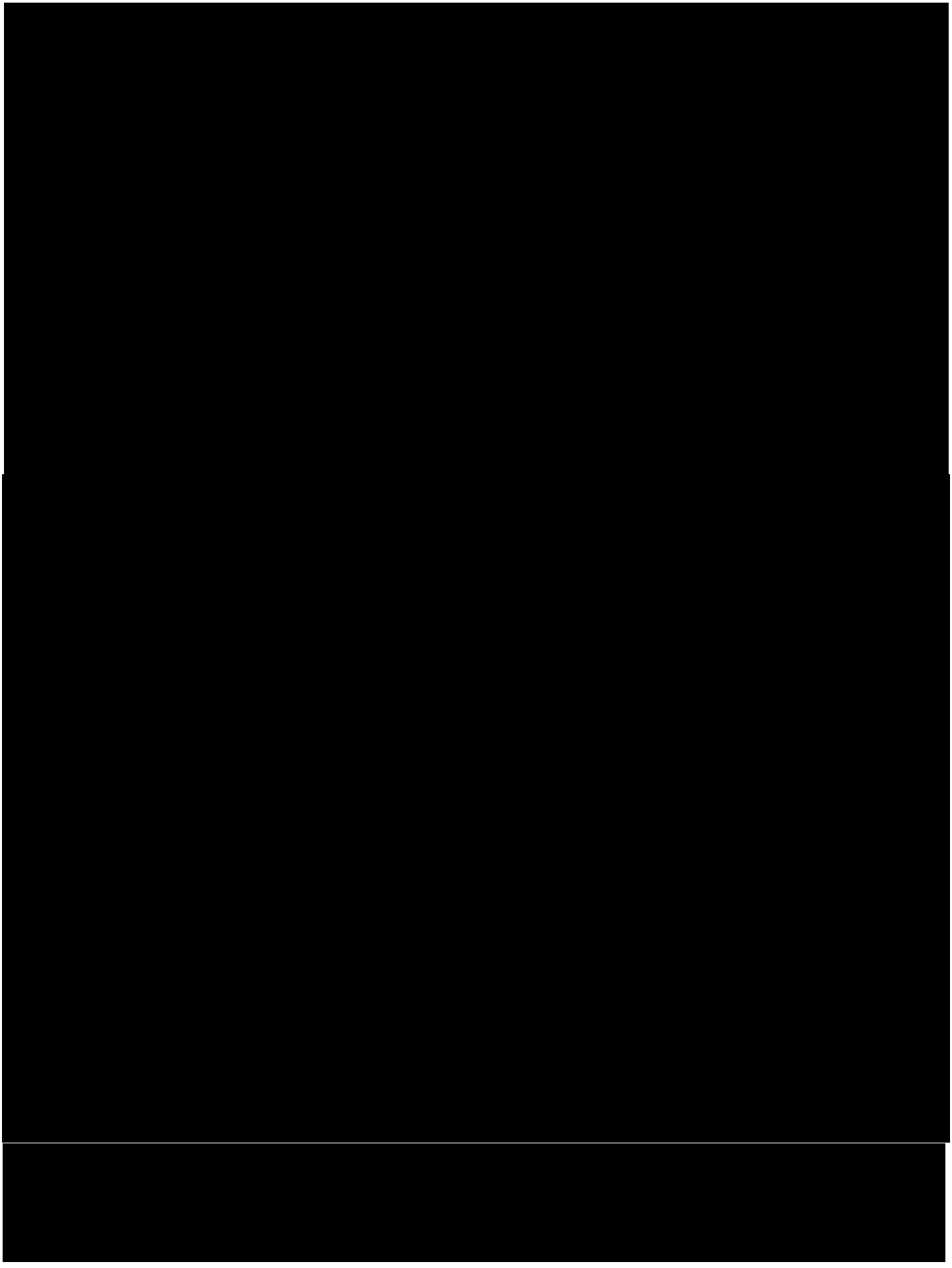
Updates to section 4.4	
Olmesartan, irbesartan, valsartan, losartan and candesartan	Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including <INN>] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.
Azilsartan, eprosartan and telmisartan	Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.
Updates to section 4.8	
Losartan, olmesartan and irbesartan	Intestinal angioedema – with an ADR frequency 'rare'
Valsartan and candesartan	Intestinal angioedema – with an ADR frequency 'very rare'

Comments:

The EMA requested the product information for olmesartan, irbesartan, valsartan, losartan and candesartan to state that cases of intestinal angioedema has been reported with their use. In contrast, the azilsartan, eprosartan and telmisartan data sheets have been updated to say that intestinal angioedema has been reported for ARBs as a class.

Of note, it is not known if the EMA's PRAC review considered if the risk of intestinal angioedema was higher with Entresto compared to ARB alone. Entresto contains an ARB with sacubitril. The latter prevents the breakdown of bradykinin which can be responsible for angioedema.

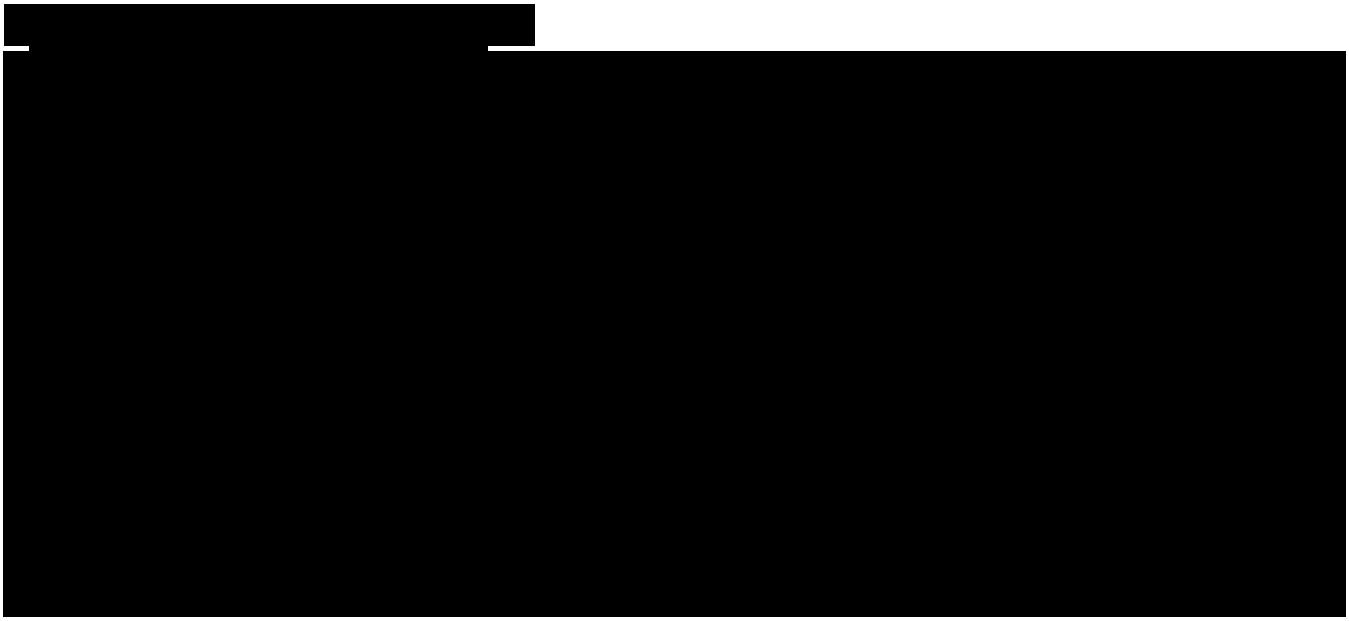
[redacted]



[redacted]

3.4 Spontaneous reports

[redacted]

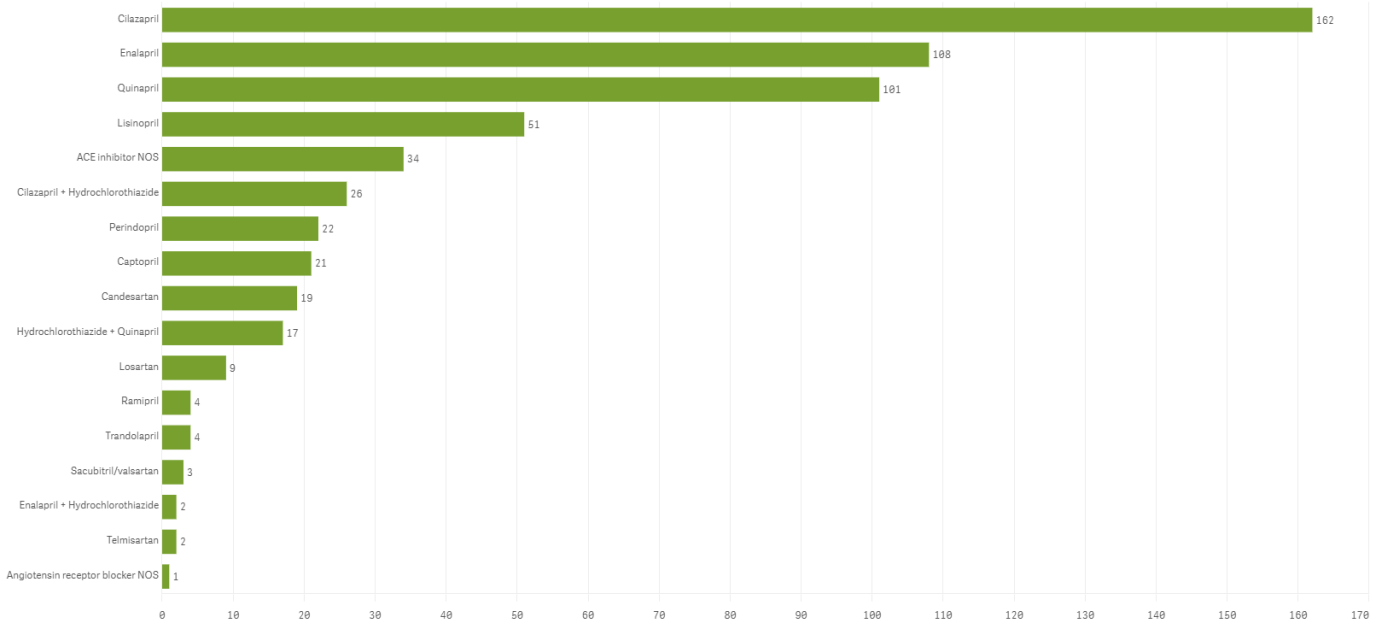


[redacted]

3.4.2 New Zealand case reports

Up to 29 July 2025, the pharmacovigilance database had received 9,516 reports where an ACEi or ARB was the suspect medicine, of which 393 reports contained the reaction term 'angioedema' (Figure 6). Although there were no cases coded with intestinal angioedema as the reaction term, related symptoms such as abdominal pain, vomiting, diarrhoea and nausea have been reported for this class of medicines.

Figure 6: Reports of angioedema with ACE inhibitors and Angiotensin II receptor blocker up to 29 July 2025



4 DISCUSSION AND CONCLUSIONS

Overview and summary of the literature

This paper reviews the risk of intestinal angioedema with ACEi and ARB.

Angioedema, although rare, is a well-known risk with ACEi, thought to be caused by a build-up of bradykinin. ARB do not affect bradykinin levels, but cases of angioedema have been reported also with this class. Angioedema will often affect the face, tongue and lips, however, angioedema can also affect the intestines. This is a presentation that may be overlooked if healthcare professionals do not consider this in their differential diagnosis.

The evidence in the literature for a link between intestinal angioedema and ACEi and ARB comes from case reports. These reports mostly involve middle aged females treated for hypertension. There were more cases involving ACEi than for ARB. Lisinopril was the most frequently reported ACEi while losartan was the most reported ARB. This pattern likely reflects usage rather than a difference in risk.

The case reports in the literature highlight that a diagnosis of intestinal angioedema is difficult to establish. This is not unexpected since this condition presents with non-specific gastrointestinal symptoms such as abdominal pain accompanied by nausea, vomiting and/or diarrhoea. These symptoms can be mistaken for other conditions such as bowel ischemia, appendicitis, inflammatory bowel disease and infectious enteritis. This means that patients may undergo invasive and unnecessary procedures.

Gastrointestinal symptoms due to ACEi/ARB induced intestinal angioedema have been reported to resolve within two to three days even without discontinuation of the medicine. This can also contribute to the condition being misdiagnosed as patients continue to take the culprit medicine for years with continual episodes of angioedema without permanent resolution.

Local and international case reports

[redacted]

Reports of intestinal angioedema from ACEi/ARB have not been received in New Zealand.

International regulatory action

The EMA's PRAC specifically reviewed the risk of intestinal angioedema with ARB. The PRAC concluded that although not all ARB were implicated in these cases, based on the established link between intestinal angioedema and other renin-angiotensin system inhibitors such as ACEi, intestinal angioedema could be considered a class effect of ARB. A class warning was imposed for ARB.

It is not known whether the EMA's PRAC considered if the risk was higher if an ARB was combined with a neprilysin inhibitor (Entresto) compared to ARB alone.

New Zealand data sheets for ACEi, ARB and Entresto

In New Zealand, all ACEi data sheets have existing information on intestinal angioedema although the level of information across this class is inconsistent. Expert advice from the Committee is sought on whether class wording for section 4.4, section 4.8, or both is needed.

For ARB, the data sheets for irbesartan and Apo-Candesartan HCTZ do not include any information on the risk of intestinal angioedema. Expert advice from the Committee is sought on whether intestinal angioedema should be considered as a side effect of ARB treatment. Depending on the Committee opinion, advice on whether data sheet changes are needed is sought.

For Entresto – neprilysin inhibitors can lead to increased bradykinin levels. Taken together with an ARB, may theoretically mean a higher risk of angioedema compared to ARB alone. In the pivotal study PARADIGM-HF (a trial designed to compare the long-term effects of Entresto with enalapril in patients with symptomatic HF

with reduced ejection fraction), angioedema was reported in 0.5% of patients treated with Entresto compared to 0.2% of patients treated with enalapril. The difference was also higher in Black patients (2.4% vs 0.5%) [41]. However, a recent observational study comparing the risk of angioedema with Entresto vs ARB and ACEi showed no observed increased risk of angioedema among new Entresto users compared with ACEi or ARB users. However, there was an increased risk of angioedema among Entresto users who recently switched from ACEi or ARB compared with Entresto new users [42]. [redacted] Expert advice from the Committee is sought if the Entresto data sheet should be updated with intestinal angioedema.

5 ADVICE SOUGHT

The Committee is asked to advise on whether:

- For ACE inhibitors
  - If the data sheets should have a consistent warning on intestinal angioedema in section 4.4?
  - If the data sheets should have intestinal angioedema as an adverse reaction (in section 4.8)?
- For ARB: if there is sufficient evidence of a class effect for ARB and intestinal angioedema?
  - If yes, should the remaining ARB data sheets be updated with a consistent warning on intestinal angioedema in section 4.4?
  - If yes, should the remaining ARB data sheets be updated with intestinal angioedema as an adverse reaction (in section 4.8)?
  - Whether the Entresto (sacubitril + valsartan) data sheet should be updated with intestinal angioedema?
- Further communication is required other than in MARC's remarks?

6 ANNEXES

[redacted]

7 REFERENCES

1. Fountain JH, Kaur J and Lappin SL. 2023. *Physiology, Renin Angiotensin System in StatPearl* 12 March 2023. URL: https://www.ncbi.nlm.nih.gov/books/NBK470410/ (accessed 6 August 2025).
2. New Zealand Formulary. 2025. *5.5.1 Angiotensin-converting enzyme inhibitors v158* 1 August 2025. URL: https://nzf.org.nz/nzf_1242 (accessed 1 August 2025).
3. Singh B, Usick AS and Goyal A. 2025. *ACE Inhibitors in StatPearls* 4 May 2025. URL: https://www.ncbi.nlm.nih.gov/books/NBK430896/ (accessed 6 August 2025).
4. bpac^{nz}. 2021. Prescribing ACE inhibitors: time to reconsider old habits. *BPJ* URL: https://bpac.org.nz/2021/ace.aspx, URL: https://bpac.org.nz/2021/ace.aspx(accessed 6 August 2025).
5. Patel P and Launico PV. 2025. *Angiotensin II Receptor Blockers (ARB) in StatPearls* 5 May 2025. URL: https://www.ncbi.nlm.nih.gov/books/NBK537027/ (accessed 6 August 2025).
6. Macaulay TE. 2007. *Cross-Reactivity of ACE Inhibitor–Induced Angioedema with ARBs in US Pharmacist* URL: https://www.uspharmacist.com/article/cross-reactivity-of-ace-inhibitorinduced-angioedema-with-arbs (accessed 6 August 2025).
7. Thalanayar PM, Ghobrial I, Lubin F, et al. 2014. Drug-induced visceral angioedema. *J Community Hosp Intern Med Perspect* 4(4): 10.3402/jchimp.v4.25260 (accessed 25 August 2025).
8. New Zealand Formulary. 2025. *2.5.5 Drugs affecting the renin-angiotensin system* 1 August 2025. URL: https://nzf.org.nz/nzf_1240 (accessed 6 August 2025).

9. Zuraw B. 2023. *An overview of angioedema: Clinical features, diagnosis, and management in UpToDate* 17 September 2023. URL: https://www.uptodate.com/contents/an-overview-of-angioedema-clinical-features-diagnosis-and-management (accessed 6 August 2025).
10. Pirahanchi Y and Sharma S. 2023. *Physiology, Bradykinin in StatPearls* 11 July 2023. URL: https://www.ncbi.nlm.nih.gov/books/NBK537187/ (accessed 6 Auust 2025).
11. Pal NL, 3rd and Fernandes Y. 2023. Intestinal Angioedema: A Mimic of an Acute Abdomen. *Cureus* 15(2): e34619. 10.7759/cureus.34619 (accessed 13 August 2025).
12. Pedroff T and Delacroix R. 2025. Recognizing Clues Associated With Angioedema of the Small Intestine: A Case Report. *Journal of Emergency Nursing* https://www.sciencedirect.com/science/article/pii/S0099176725001424, https://doi.org/10.1016/j.jen.2025.04.012https://doi.org/10.1016/j.jen.2025.04.012 (accessed 13 August 2025).
13. Gillion V, Dragean CA, Dahlqvist G, et al. 2019. Intestinal angioedema from angiotensin converting enzyme inhibitor. *Kidney International* 96(3): 798. 10.1016/j.kint.2019.02.031 (accessed 13 August 2025).
14. Parreira R, Amaral R, Amaral L, et al. 2020. ACE inhibitor-induced small bowel angioedema, mimicking an acute abdomen. *J Surg Case Rep* 2020(10): rjaa348. 10.1093/jscr/rjaa348 (accessed 13 August 2025).
15. Voore N and Stravino V. 2015. Isolated small bowel angio-oedema due to ACE inhibitor therapy. *BMJ Case Reports* 2015(bcr2015212623. 10.1136/bcr-2015-212623 (accessed 13 August 2025).
16. Sravanthi MV, Suma Kumaran S, Sharma N, et al. 2020. ACE inhibitor induced visceral angioedema: an elusive diagnosis. *BMJ Case Rep* 13(11): 10.1136/bcr-2020-236391 (accessed 13 August 2025).
17. Weingärtner O, Weingärtner N, Böhm M, et al. 2009. Bad gut feeling: ACE inhibitor induced intestinal angioedema. *BMJ Case Reports* 2009(bcr0920080868. 10.1136/bcr.09.2008.0868 (accessed 13 August 2025).
18. Campbell T, Peckler B, Hackstadt R, et al. 2010. ACE Inhibitor-Induced Angioedema of the Bowel. *Case reports in medicine* 2010(690695. 10.1155/2010/690695 (accessed 13 August 2025).
19. Kale S. 2024. ACE inhibitor induced small bowel angioedema. *Journal of Clinical Images and Medical Case Reports* 5(5), doi: www.doi.org/10.52768/2766-7820/3065(accessed 13 August 2025).
20. Wilin KL, Czupryn MJ, Mui R, et al. 2018. ACE Inhibitor-Induced Angioedema of the Small Bowel: A Case Report and Review of the Literature. *Journal of Pharmacy Practice* 31(1): 99-103. 10.1177/0897190017690641 (accessed 13 August 2025).
21. Augenstein VA, Heniford BT and Sing RF. 2013. Intestinal Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: An Underrecognized Cause of Abdominal Pain? *Journal of Osteopathic Medicine* 113(3): 221-223. doi:10.7556/jaoa.2013.113.3.221 (accessed 13 August 2025).
22. Niyibizi A, Cisse MS, Rovito PF, et al. 2023. Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Angioedema of the Small Bowel: A Diagnostic Dilemma. *J Am Board Fam Med* 36(1): 160-163. 10.3122/jabfm.2022.220276R1 (accessed 13 August 2025).
23. Lee MN. 2022. *Case Study: Review of ACE Inhibitor-Induced Bowel Angioedema* 9 August 2022. URL: https://www.pharmacytimes.com/view/case-study-review-of-ace-inhibitor-induced-bowel-angioedema (accessed 13 August 2025).
24. Gabriel J, Vedantam V, Kapila A, et al. 2018. Recognizing a Rare Phenomenon of Angiotensin-Converting Enzyme Inhibitors: Visceral Angioedema Presenting with Chronic Diarrhea—A Case Report. *The Permanente Journal* 22(1): 17-030. doi:10.7812/TPP/17-030 (accessed 13 August 2025).
25. Byrne TJ, Douglas DD, Landis ME, et al. 2000. Isolated Visceral Angioedema: An Underdiagnosed Complication of ACE Inhibitors? *Mayo Clinic Proceedings* 75(11): 1201-1204. https://doi.org/10.4065/75.11.1201 (accessed 13 August 2025).
26. Marmery H and Mirvis SE. 2006. Angiotensin-converting enzyme inhibitor-induced visceral angioedema. *Clinical Radiology* 61(11): 979-982. https://doi.org/10.1016/j.crad.2006.06.010 (accessed 13 August 2025).
27. Inayat F and Hurairah A. 2016. Small Bowel Angioedema Secondary to Angiotensin-Converting Enzyme Inhibitors. *Cureus* 8(12): doi: 10.7759/cureus.943 (accessed 13 August 2025).

28. Korniyenko A, Alviar CL, Cordova JP, et al. 2011. Visceral angioedema due to angiotensin-converting enzyme inhibitor therapy. *Cleve Clin J Med* 78(5): 297-304. 10.3949/ccjm.78a.10102 (accessed 13 August 2025).
29. Oliveira AM, Santiago I, Carvalho R, et al. 2016. Isolated Visceral Angioedema Induced by Angiotensin-Converting Enzyme Inhibitor. *GE Port J Gastroenterol* 23(3): 162-165. 10.1016/j.jpge.2015.09.008 (accessed 13 August 2025).
30. Krause AJ, Patel NB and Morgan J. 2019. An unusual presentation of ACE inhibitor-induced visceral angioedema. *BMJ Case Reports* 12(9): e230865. 10.1136/bcr-2019-230865 (accessed 13 August 2025).
31. Savino MR, Mittal PK and Miller FH. 2017. MR imaging of intestinal angioedema related to angiotensin-converting enzyme inhibitors: Report of three cases and review of literature. *Clin Imaging* 43(122-126. 10.1016/j.clinimag.2017.03.001 (accessed 13 August 2025).
32. Huynh TNA, Hua L, Smalberger JA, et al. 2022. ACE inhibitor induced intestinal angioedema. *ANZ J Surg* 92(11): 3110-3111. 10.1111/ans.17575 (accessed 13 August 2025).
33. Pinto MB, Vecchio M and Santos MA. 2022. A Gut Feeling: Isolated Small Bowel Angioedema due to Angiotensin-Converting Enzyme Inhibitor. *R I Med J (2013)* 105(6): 28-31. (accessed 13 August 2025).
34. Pirzada S, Raza B, Mankani AA, et al. 2023. A Case of Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Small Bowel Angioedema. *Cureus* 15(10): e47739. 10.7759/cureus.47739 (accessed 13 August 2025).
35. Adam M, Tselovalnikova T and Evans A. 2025. Another Crohn's Disease Mimicker: A Case of Angiotensin-Converting Enzyme Inhibitor-Induced Intestinal Angioedema. *ACG Case Rep J* 12(2): e01608. 10.14309/crj.0000000000001608 (accessed 13 August 2025).
36. Almedida CL, Ghezzi TL and Corleta OC. 2017. *Angiotensin-converting enzyme inhibitors-induced angioedema of the small bowel mimicking postoperative complication* URL: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-01082017000600029 (accessed 13 August 2025).
37. Mousa O, Sacco K and Wang M-H. 2016. Losartan-Induced Intestinal Angioedema: 2169. *Official journal of the American College of Gastroenterology | ACG* 111(S1035-S1036. https://journals.lww.com/ajg/fulltext/2016/10001/losartan_induced_intestinal_angioedema__2169.2169.aspx(accessed 13 August 2025).
38. Rosas S, Fowler A, Stodgill E, et al. 2023. A Rare Case of Losartan-Induced Visceral Angioedema. *Journal of Primary Care & Community Health* 14(21501319231213744. 10.1177/21501319231213744 (accessed 13 August 2025).
39. Hanefeld-Fox L, Jimenez L, Heflin R, et al. 2018. Sacubitril/Valsartan-Associated Small Bowel Ileus. *Am J Ther* 25(6): e705-e706. 10.1097/mjt.0000000000000720 (accessed 13 August 2025).
40. European Medicines Agency. 2024. *Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of PRAC meeting on 8-11 July 2024 EMA/PRAC/337971/2024* 23 August 2024. URL: https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-8-11-july-2024_en.pdf (accessed 6 August 2025).
41. Novartis. 2022. *New Zealand Entresto Data Sheet* 7 December 2022. URL: https://www.medsafe.govt.nz/profs/datasheet/e/entrestotab.pdf (assessed 25 August 2025).
42. Eworuke E, Welch EC, Haug N, et al. 2023. Comparative Risk of Angioedema With Sacubitril-Valsartan vs Renin-Angiotensin-Aldosterone Inhibitors. *JACC* 81(4): 321-331. doi:10.1016/j.jacc.2022.10.033 (accessed 25 August 2025).