Medicines & Healthcare products Regulatory Agency

DRUG SAFETY UPDATE (DSU)

ACE-inhibitors: Be aware of the distinction between bradykinin- and histamine-mediated angioedema, as treatment strategies differ significantly

Specialisms: *Cardiovascular disease, General Practice, Emergency medicine, Pharmacy and Nephrology*

Summary

The product information for all ACE inhibitors is being updated to strengthen the warnings on the risk of delayed-onset angioedema, which may still occur after weeks to years of use. Healthcare professionals, particularly in emergency departments, should be aware of the potential for delayed onset of angioedema and the distinction between bradykinin- and histamine-mediated cases, as treatment strategies differ significantly and bradykinin-mediated angioedema does not respond to standard treatment.

Advice for Healthcare Professionals:

- angioedema is a known uncommon or rare side-effect of ACE inhibitor treatment. This can either be allergic (histamine-mediated) or less commonly non-allergic (bradykinin-mediated). Healthcare professionals should consider bradykinin-mediated mechanisms as a cause when standard anaphylaxis treatment is ineffective
- angioedema can occur at any time during treatment, including after weeks to years of use
- swelling of the tongue, lip, face, or larynx which may cause difficulty in breathing or swallowing may progress and can lead to airway compromise. Other symptoms can include gastrointestinal pain and cramps[1]
- bradykinin-mediated angioedema is unlikely to respond to standard anaphylaxis treatments including adrenaline (epinephrine)
- lack of response to standard anaphylaxis treatments should prompt consideration of bradykinin-mediated angioedema, with treatment informed by clinical protocols

- if angioedema is suspected in a patient taking an ACE inhibitor, discontinue the ACE inhibitor immediately and do not restart

Advice for Healthcare Professionals to Provide to Patients:

- although uncommon or rare, angioedema (swelling of the face, lips, tongue, or throat) can occur at any time while taking an ACE inhibitor, even if you have been taking it for a long period without problems
- seek urgent medical attention if you develop swelling of the face, lips, tongue, or throat, or experience difficulty breathing or swallowing whilst taking ACE inhibitors
- do not take further doses of your ACE inhibitor if angioedema is suspected and inform a healthcare professional immediately
- inform healthcare professionals if you have ever experienced angioedema, including while taking an ACE inhibitor. Please be aware that angioedema can occur for other reasons, and a healthcare professional may still recommend an ACE inhibitor for you in these instances

Background

ACE inhibitors are indicated for the treatment of hypertension, heart failure, post-myocardial infarction management, diabetic nephropathy, and cardiovascular risk reduction.

Angioedema is characterised by localised swelling of subcutaneous or submucosal tissues. Unlike histamine-mediated (allergic) angioedema, bradykinin-mediated angioedema usually occurs without urticaria and typically has a slower onset. Symptoms may involve the tongue, lips, and upper airway, and can be life-threatening.

Although uncommon or rare, ACE inhibitors are associated with both histamine-mediated and bradykinin-mediated angioedema. Certain populations, including older adults, women, people who smoke and patients of Black or African Caribbean ethnicity, may be at increased risk of angioedema.

Data review

A review of UK Yellow Card data up to and including 10 June 2026 identified that approximately one-half of angioedema cases with reported time-to-onset occurred 30 days or more after initiation of treatment. Manufacturer data indicated that around 20–30% of reported cases occurred after at least 30 days of therapy. This pattern of delayed onset is more associated with bradykinin-mediated angioedema. Fatal cases, although rare, have involved airway compromise and have occurred after prolonged ACE inhibitor treatment.

Published literature describes bradykinin–mediated angioedema occurring weeks to many years after initiation, including cases reported after several years of continuous use[2, 3]. Reviews consistently highlight that bradykinin-mediated angioedema does not reliably respond to standard anaphylaxis treatment and requires prompt recognition and appropriate airway management[4].

Current clinical guidance used in emergency medicine recognises ACE inhibitors as a leading cause of non-allergic angioedema and advises consideration of bradykinin-mediated mechanisms when standard treatment is ineffective. The clinical guidance emphasises prompt discontinuation of the ACE inhibitor, close airway monitoring, and early specialist involvement in severe or life-threatening cases. Additional investigations, such as C4 level testing, may support identification of non-allergic causes and help guide management. [5, 6]

Regulatory action

The MHRA is implementing updates to the Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) in a phased approach. The SmPC and PIL for ACE inhibitors will be updated to strengthen warnings and improve communication on the risk of delayed-onset angioedema and the potential for standard anaphylaxis treatments to be ineffective. These updates are currently in progress and will be implemented over the coming months.

Reporting advice

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website.
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

Additional information

You can sign up to receive email notifications for Drug Safety Updates.

You can sign up to receive our monthly roundup of safety communications.

For any enquiries, please contact info@mhra.gov.uk

References

1. https://cks.nice.org.uk/topics/angio-oedema-anaphylaxis/management/angio-oedema-without-anaphylaxis/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8966254/
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8031276/
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9803396/
5. Chronic Urticaria and Angioedema - BSACI
6. https://www.rcemlearning.co.uk/reference/angioedema/#1568108920792-812b7e84-9e19

Stakeholder engagement:

- NHS England Patient Safety and Devolved Administrations
- Royal College of Emergency Medicine (RCEM)
- NHS Specialist Pharmacy Service

Article citation: MHRA Drug Safety Update volume 19, issue 11: June 2026: 1