Safety Alert

August. 2026

Captopril – Insulin autoimmune syndrome and Angioedema

EDA performs label update to include the following:

Special warnings and precautions for use :

Hypersensitivity/angioedema:

Angioneurotic oedema of the extremities, face, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors particularly during the first week of treatment. However, in rare cases, severe angioedema may develop after months or years of long-term treatment with an ACE inhibitor.

Insulin Autoimmune Syndrome (IAS):

Cases of Insulin Autoimmune Syndrome (IAS), including severe hypoglycemic events have been reported during the treatment with captopril . If IAS is suspected, captopril should be discontinued, and appropriate treatment should be initiated.

Undesirable effects :

Immune System Disorder'

Insulin autoimmune syndrome : frequency – not known

Background:

Angioedema is deep-tissue swelling of the skin or mucous membranes caused by transient fluid leakage from blood vessels. It is classified into two primary types based on the underlying mechanism:

- Allergic (Histamine): Fast onset, causes itching/hives, treated with antihistamines or epinephrine.

- Non-Allergic (Bradykinin): Caused by medications (like ACE inhibitors) or genetics (Hereditary Angioedema). No hives or itching; requires specialized treatment.

Insulin Autoimmune Syndrome (IAS), or Hirata's Disease, is a rare autoimmune condition causing unpredictable low blood sugar (hypoglycemia) in individuals with no history of external insulin use.

Triggers: Commonly induced by exposure to sulfhydryl (-SH) group-containing drugs or supplements (e.g., alpha-lipoic acid, methimazole, captopril).

Key Diagnostic Biomarkers for IAS :

- Positive IAA: High levels of antibodies targeting endogenous (self-produced) insulin.

- Markedly High Insulin: Paradoxically elevated serum insulin during hypoglycemic episodes.

- Elevated C-Peptide: Confirms high insulin originates from the body's pancreas, ruling out synthetic insulin administration.

Key Characteristics:

For Angioedema :

- **Nature:** Deep-tissue, non-pitting swelling (face, lips, tongue, throat, GI tract).
- **Airway Danger:** Laryngeal edema can cause life-threatening asphyxiation.
- **Histamine vs. Bradykinin Type:**

Histamine (Allergic): Fast onset, has hives/itching, responds to epinephrine and antihistamines.

Bradykinin (Non-Allergic): Gradual onset, no hives/itching, resistant to allergy medications .

For Angioedema :

- **Spontaneous Hypoglycemia:** Episodes usually occur a few hours after eating (postprandial).
- **Antibody-Driven Mechanism**: Autoantibodies bind naturally secreted insulin, keeping it inactive. Later, these antibodies release large amounts of insulin all at once, causing a sudden drop in blood sugar.
- **Self-Limiting Nature:** It typically resolves on its own within 3 to 6 months after stopping the triggering medication or adjusting to a low-carbohydrate, small-meal diet.

Therapeutic Indications :

Captopril is indicated for:

- **Hypertension**: Mild to moderate hypertension (first-line/standard use); severe hypertension when standard therapies fail or are unsuitable.
- **Congestive Heart Failure**: Used as add-on therapy alongside diuretics (and digitalis/beta-blockers where appropriate).
- **Myocardial Infarction (Post-MI)**:
  - Short-term (4 weeks): Clinically stable patients within 24 hours of an infarction.
  - Long-term prevention: Clinically stable patients with asymptomatic left ventricular dysfunction (ejection fraction ≤ 40%) to reduce mortality, heart failure hospitalizations, recurrent MIs, and revascularization procedures. Pre-treatment cardiac imaging (echocardiogram or radionuclide ventriculography) is required.
- **Type I Diabetic Nephropathy**:Captopril is indicated in insulin dependent diabetics for the treatment of macroproteinuric diabetic nephropathy .

Reference

EMA (click Here)