ACETAZOLAMIDE

THERAPEUTICS

Brands
- Diamox, Diamox-Sequels, Azomid, AZM, Dazamide, Novo-Zolamide

Generic?
- Yes

Class
- Antiepileptic drug (AED)

Commonly Prescribed for
(FDA approved in bold)
- **Adjunctive treatment for centrencephalic epilepsies (petit mal, unlocalized)**
- **Acute mountain sickness**
- **Edema due to congestive heart failure or medication**
- **Glaucoma**
- Adjunctive treatment for generalized tonic-clonic and partial seizures
- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebrii)
- Episodic ataxias type 1 and 2
- Hemiplegic migraine
- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
- Marfan syndrome
- Sleep apnea

How the Drug Works
- Blocks the carbonic anhydrase enzyme, which is responsible for converting carbon dioxide and water to bicarbonate. This increases excretion of sodium, potassium, bicarbonate, and water, producing alkaline diuresis. In epilepsy, it decreases excessive neuronal discharge in CNS due to either slight degree of acidosis or perhaps reduction of extracellular calcium. It also reduces production of CSF and aqueous humor

How Long Until It Works
- Seizures: within a few days
- IIH: maximum benefit in 4–6 weeks

If It Works
- Seizures: goal is the remission of seizures. Continue as long as effective and well tolerated. Consider tapering and slowly stopping after 2 years seizure-free, depending on the type of epilepsy
- IIH: monitor visual fields and papilledema and symptoms such as visual obscurations and headache

If It Doesn't Work
- Increase to highest tolerated dose
- Seizures: consider changing to another agent, adding a second agent, using a medical device, or a referral for epilepsy surgery evaluation. When adding a second agent, keep drug interactions in mind
- IIH: eliminate symptomatic causes such as drugs or toxins, encourage weight loss if patient is obese, consider loop diuretics or topiramate. Lumbar puncture often provides short-term relief of symptoms. For visual loss, optic nerve defenestration or CSF shunting (lumboperitoneal or ventriculoperitoneal) may be needed

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Epilepsy: acetazolamide itself is usually an augmenting agent. Relatively few interactions with other AEDs. Topiramate and zonisamide have similar mechanisms of action, so acetazolamide is not usually combined with these agents
- IIH: furosemide and topiramate may be helpful. Combine with caution due to risk of kidney stone formation

Tests
- Obtain a CBC when starting drug and during therapy. Check bicarbonate, potassium, and sodium levels if symptoms of metabolic acidosis develop

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Related to carbonic anhydrase inhibition, which can cause metabolic acidosis and electrolyte imbalances

Notable AEs
- Paresthesias, tinnitus, sedation, GI disturbance (anorexia, nausea/vomiting, diarrhea, taste alteration, appetite suppression, weight loss), myopia

(transient), renal calculi, frequent urination, and photosensitivity

Life-Threatening or Dangerous AEs

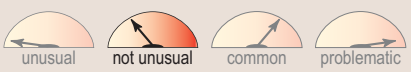
- Blood dyscrasias (agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia). Hypokalemia. Rash including Stevens-Johnson syndrome. Fulminant hepatic necrosis

Weight Gain

- Unusual

Sedation

- Not unusual



What to Do About AEs

- Lower dose when used for epilepsy or IIH. If AEs are significant, discontinue and change to another agent. Paresthesias may respond to high-potassium diets or potassium supplements

Best Augmenting Agents to Reduce AEs

- Concomitant topiramate, zonisamide, ketogenic diet predisposes to metabolic acidosis and kidney stones. Metformin may also promote acidosis

DOSING AND USE

Usual Dosage Range

- Epilepsy: age > 12: 375–1000 mg daily. Age < 12: 10–20 mg/kg/day. catamenial: 8~30 mg/kg/day
- IIH: 250–2000 mg daily
- Edema: 250–375 mg every other day
- Mountain sickness: 500–1000 mg daily

Dosage Forms

- Tablets: 125, 250 mg. Sustained release 500 mg
- Injection: 500 mg vials

How to Dose

- Epilepsy: start at 125–250 mg twice daily, with a lower starting dose (250 mg daily) for patients already on other AEDs. Occasionally used at higher doses, but not necessarily more effective
- IIH: start at 250–500 mg/day in 2 divided doses. Increase as tolerated to 1000 mg/day. Occasionally used at higher doses, depending on tolerability and effect on visual symptoms
- Acute mountain sickness: start 24–48 hours before ascent and continue for 48 hours or as long as needed to control symptoms. Usual dose 250–1000 mg/day
- Congestive heart failure: 250–375 mg daily, skipping doses every 2–3 days to maintain effect

Dosing Tips

- Citrus juice and fluids may help decrease risk of kidney stone formation. Taking with food can decrease AEs

Overdose

- Ataxia, anorexia, nausea, paresthesias, vomiting, tremor, and tinnitus. Induce emesis or gastric lavage. Supplement with bicarbonate or potassium as necessary

Long-Term Use

- Safe for long-term use. Tolerance due to increased carbonic anhydrase production in glial cells

Habit Forming

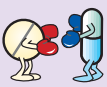
- No

How to Stop

- Taper slowly
- Abrupt withdrawal can lead to seizures in patients with epilepsy
- Papilledema or headaches may recur within days to months of stopping

Pharmacokinetics

- Tablets have peak effect at 2–4 hours, with 8–12 hours duration of action. Sustained-release tablets have peak effect at 3–6 hours and duration of 18–24 hours. 70–90% protein bound. Not metabolized and excreted unchanged by kidneys



Drug Interactions

- Not affected by other AEDs
- Decreases levels of primidone, lithium
- Increases levels of cyclosporine, carbamazepine, phenytoin, phenobarbital
- Concurrent use with salicylates can increase AEs of both
- Prolongs effects of amphetamines, quinidine

Do Not Use

- Known hypersensitivity to the drug. Depressed potassium or sodium levels, significant kidney or hepatic disease, hyperchloremic acidosis, adrenocortical insufficiency, and suprarenal gland dysfunction

Other Warnings/ Precautions

- Carbonic anhydrase inhibitors are sulfonamides. There may be cross-sensitivity with antibacterial sulfonamides. Increased risk of hyponatremia when combined with carbamazepine or oxcarbazepine

SPECIAL POPULATIONS

Renal Impairment

- Renal insufficiency can lead to increased toxicity. Use with caution

Hepatic Impairment

- Use with caution. Patients with severe disease have an increased risk of hyperammonemia or bleeding complications

Cardiac Impairment

- Severe hypokalemia causes cardiac arrhythmias. Chronic metabolic acidosis may lead to hyperventilation and decreases left ventricular function – use with caution in patients on β-blocker or calcium channel therapy

Elderly

- Use with caution

Children and Adolescents

- Safety and effectiveness in the pediatric population is unknown. Suggested daily dose is 8–30 mg/kg

Pregnancy

- Category C. Risks of stopping medication must outweigh risk to fetus for patients with epilepsy. Seizures and potential status epilepticus place the woman and fetus at risk and can cause reduced oxygen and blood supply to the womb
- In IIH, consider lumbar puncture as an alternative to medication, especially in the first few months of pregnancy, and monitor closely for visual changes
- Supplementation with 0.4 mg of folic acid before and during pregnancy is recommended

Breast Feeding

- A small percentage is excreted in breast milk. Monitor infant for sedation, poor feeding, or irritability

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Inexpensive adjunctive medication for epilepsy and useful in the treatment of IIH and episodic ataxias. Rapid onset of action

Potential Disadvantages

- Not a first-line drug in epilepsy or migraine due to ineffectiveness and AEs. Tolerance

Primary Target Symptoms

- Seizure frequency and severity; headache or papilledema in IIH

Pearls

- In epilepsy, appears most effective in children with petit mal epilepsy, but may be effective in patients with grand mal, mixed, or myoclonic seizures
- Acetazolamide was used for migraine aura status in case reports

ACETAZOLAMIDE (continued)

- Acetazolamide is occasionally used for treatment of migraine. Large, double-blind, placebo-controlled trials did not indicate effectiveness
- First-line for IIH by lowering the CSF production. In a recent trial comparing 6 months of acetazolamide (up to 4 g/day) to placebo, significant improvements were found in visual field function and papilledema but with 19% dropout. It did not appear to reduce associated headache
- In an open-label study on IIH, topiramate was as effective as acetazolamide but with prominent weight loss, which is beneficial for treating IIH
- In patients under topiramate or metformin, spironolactone can be an alternative
- First-line agent for treatment of episodic ataxias at an average dose of 500–750 mg/day. Type 2 responds better than type 1 in most cases
- Similar to episodic ataxia type 2, familial hemiplegic migraine type 1 is a channelopathy caused by a mutation of the *CACNA1A* gene. Case reports suggest acetazolamide can be used to treat hemiplegic migraine
- Found to be dramatically effective in a subset of MELAS patients with episodic weakness associated with specific mitochondrial DNA mutations
- As a diuretic, increased doses do not increase effect. Results are often improved with alternating days of treatment
- The acetazolamide challenge test is used to decide indications for CSF shunting
- Good for intermittent use, such as in catamenial epilepsy

Suggested Reading

Auré K, Dubourg O, Jardel C, Clarysse L, Sternberg D, et al. Episodic weakness due to mitochondrial DNA MT-ATP6/8 mutations. *Neurology*. 2013;81(21):1810–18.

Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatry*. 2012;83(5):488–94.

Kayser B, Dumont L, Lysakowski C, Combescure C, Haller G, Tramèr MR. Reappraisal of acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis. *High Alt Med Biol*. 2012;13 (2):82–92.

Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia*. 2002;43(10):1168–71.

Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. *Ann Pharmacother*. 1996;30(5):514–19.

Robbins MS, Lipton RB, Laureta EC, Grosberg BM. CACNA1A nonsense mutation is associated with basilar-type migraine and episodic ataxia type 2. *Headache*. 2009;49(7):1042–6.

Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA*. 2014;311(16):1641–51.

ALEMTUZUMAB

THERAPEUTICS

Brands
- Lemtrada, Campath, MabCampath, Campath-1H

Generic?
- No

Class
- Immunosuppressant

Commonly Prescribed for
(FDA approved in bold)
- **Relapsing forms of multiple sclerosis (MS)**
- **B-cell chronic lymphocytic leukemia (B-CLL)**
- Induction therapy in organ transplantation
- Sporadic inclusion body myositis (sIBM)

How the Drug Works
- It is a humanized IgG_1 kappa antibody that targets cell-surface glycoprotein CD52, which is expressed at a high level on T and B lymphocytes. Upon binding, it induces antibody-dependent cellular cytolysis and complement-mediated lysis of T and B lymphocytes. It particularly targets CD4+ naïve and CD8+ naïve T cells, and mature naïve B cells with proportional increase in regulatory T cells and memory T/B cells. Lymphocyte counts decrease after each course of treatment. Cells that escaped depletion may cause secondary autoimmunity. It also has prolonged decrease in the secretion of proinflammatory cytokines (interleukin [IL]-17, IL-22)

How Long Until It Works
- Months to years. In trials, treated patients had fewer relapses up to 2–5 years

If It Works
- Continue to use until ineffective. Screen for AEs

If It Doesn't Work
- It is the third-line treatment for relapsing forms of MS. If it fails, consider combination therapy with other disease-modifying agents

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Acute MS attacks are often treated with glucocorticoids, especially if there is functional impairment due to vision loss, weakness, or cerebellar symptoms
- Treat common clinical symptoms with appropriate medication for spasticity (baclofen, tizanidine), neuropathic pain, and fatigue (modafinil)
- It is uncertain whether combined use of 2 types of antibodies or adding another disease-modifying agent is beneficial to MS

Tests
- CBC and platelet counts (monthly), thyroid function tests (every 3 months), and renal function (regularly) until 4 years after the last infusion. Yearly skin exams

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Most AEs are likely related to immunosuppression or hypersensitivity

Notable AEs
- Rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes infection, thyroid gland disorder, fungal infection, arthralgia, back pain, diarrhea, paresthesia, dizziness, abdominal pain, flushing, vomiting

Life-Threatening or Dangerous AEs
- Thyroid disorders (20%)
- Immune thrombocytopenic purpura
- Anti-glomerular basement membrane disease
- Leukopenia, pancytopenia
- Severe infection
- Anaphylaxis
- Increased risk of malignancy (thyroid cancer, melanoma, lymphoproliferative disorder)

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Control infection. Supportive treatment

Best Augmenting Agents to Reduce AEs
- Most AEs will not respond to augmenting agents

DOSING AND USE

Usual Dosage Range
- A total of 96 mg is the standard dose for MS

Dosage Forms
- Injection: 12 mg/1.2 mL, 30 mg/1 mL in a single-use vial

How to Dose
Lemtrada (for MS)
- First course: 12 mg/day on 5 consecutive days. IV infusion over 4 hours
- Second course (1 year after): 12 mg/day on 3 consecutive days
- It is available only through a restricted distribution program called the Lemtrada Risk Evaluation and Mitigation Strategy (REMS) Program
- Premedicate with corticosteroid for the first 3 days of each course
- Herpes prophylaxis for a minimum of 2 months after each course or until CD4+ lymphocyte count is $> 200/mm^3$, whichever occurs later

Campath (for B-CLL)
- Escalate to recommended dose of 30 mg/day 3 times per week for 12 weeks. IV infusion over 2 hours
- Premedicate with oral antihistamine and acetaminophen prior to dosing
- Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections

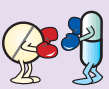
Overdose
- Doses greater than those recommended may increase the intensity and/or duration of infusion reactions or its immune effects. There is no known antidote for alemtuzumab overdosage

Long-Term Use
- Risk of infection, autoimmunity, and malignancy. Use beyond the approved dose or term is not recommended

Habit Forming
- No

How to Stop
- No need to taper

Pharmacokinetics
- Alemtuzumab serum concentrations reach maximum at the last day of infusion. It is largely confined to the blood and interstitial space. It is degraded by widely distributed proteolytic enzymes. Half-life 2 weeks



Drug Interactions
- No formal drug interaction studies have been conducted. Increases risk of serious infection when used with other immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, and 6-mercaptopurine) or inhibitors of tumor necrosis factor-α (TNF-α)

Other Warnings/ Precautions
- Infusion reactions usually occur within 2 hours but some reactions were reported after 24 hours
- Because of risk of autoimmunity, infusion reactions, and the risk of some kinds of cancers, Lemtrada is only available through the Lemtrada REMS Program

Do Not Use
- Hypersensitivity to drug. Severe infection. HIV

SPECIAL POPULATIONS

Renal Impairment
- May cause anti-glomerular basement membrane disease

Hepatic Impairment
- Not studied

Cardiac Impairment
- Does not prolong QTc interval

Elderly
- Not studied

Children and Adolescents
- It is not known if it is safe and effective for use in children under 17 years of age

Pregnancy
- Category C. Placental transfer of antithyroid antibodies resulting in neonatal Graves' disease has been reported. Use only if benefit of preventing MS relapse outweighs risk. Women of childbearing potential should use effective contraceptive measures when receiving a course of treatment with alemtuzumab and for 4 months following that course of treatment

Breast Feeding
- It is excreted in breast milk. Do not breast feed on drug

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Effective treatment for some of the most disabled MS patients including those failing first-line agents. Efficacy may be superior to other disease-modifying agents

Potential Disadvantages
- Rare but potentially fatal AEs of autoimmunity, opportunistic infection, and malignancy. Only available through specific infusion centers as IV infusion. Need for long-term monitoring

Primary Target Symptoms
- Decrease in relapse rate, prevention of disability, and slower accumulation of lesions on MRI

Pearls
- At this point, due to potentially severe AEs, it is usually reserved for patients with a very severe form of relapsing MS who have failed 2 types of disease-modifying treatments and are not candidates for natalizumab
- May be an alternative to natalizumab in patients with JC virus antibodies
- In clinical trials, the lowest cell counts occurred 1 month after a course of treatment at the time of the first post-treatment blood count. Lymphocyte counts then increased over time: B-cell counts usually recovered within 6 months; T-cell counts increased more slowly and usually remained below baseline 12 months after treatment. Approximately 60% of patients had total lymphocyte counts below the lower limit of normal 6 months after each treatment course and 20% had counts below the lower limit of normal after 12 months
- It is also approved for relapsing-remitting MS with superior 2-year relapse-free rate and reduced disability progression than interferon-β (INFβ)-1a in previously treated patients; superior 2-year relapse-free rate than INFβ-1a in treatment-naïve patients. The efficacy appears to continue beyond treatment period. However, it was associated with greater side effects (infection, malignancy, thyroid disorder, autoimmunity, thrombocytopenic purpura)
- Given higher rates of remission compared to INFβ-1a and -1b, might eventually have a place as an induction therapy prior to initiation of other agents
- In successfully treated patients consider initiating other treatment only after lymphocyte counts have normalized
- CAMMS223: alemtuzumab remained significantly more efficacious than INFβ-1a up to 5 years of study period
- In a small trial of 13 sIBM patients, alemtuzumab 0.3 mg/kg/day for 4 days slows the disease progression up to 6 months, improves the strength of some patients, and reduces endomysial inflammation and stressor molecules. Bimagrumab (activin receptor II antibody) is another investigational drug showing promising results on increasing muscle mass and function

Suggested Reading

Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 Clinical Trial. *Neurology*. 2012;78(14):1069–78.

Cossburn M, Pace AA, Jones J, Ali R, Ingram G, Baker K, et al. Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. *Neurology*. 2011;77(6):573–9.

Dalakas MC, Rakocevic G, Schmidt J, Salajegheh M, McElroy B, Harris-Love MO, et al. Effect of Alemtuzumab (CAMPATH 1-H) in patients with inclusion-body myositis. *Brain*. 2009;132(6):1536–44.

Garnock-Jones KP. Alemtuzumab: a review of its use in patients with relapsing multiple sclerosis. *Drugs*. 2014;74(4):489–504.

Zhang X, Huang H, Han S, Fu S, Wang L. Alemtuzumab induction in renal transplantation: a meta-analysis and systemic review. *Transpl Immunol*. 2012;27(2-3):63–8.

ALMOTRIPTAN

THERAPEUTICS

Brands
- Axert, Almogran

Generic?
- Yes

Class
- Triptan

Commonly Prescribed for
(FDA approved in bold)
- **Acute treatment of migraine in adults and adolescents (> 12 years old)**
- Menstrual migraine

How the Drug Works:
- Selective 5-$HT_{1B/1D/1F}$ receptor agonist. In addition to vasoconstriction on meningeal vessels, its antinociceptive effect is likely due to blocking the transmission of pain signals at trigeminal nerve terminals (preventing the release of inflammatory neuropeptides) and synapses of second-order neurons in trigeminal nucleus caudalis. Although it generally does not penetrate BBB, it has been postulated that transient permeability may occur during a migraine attack

How Long Until It Works
- 1–2 hours or less

If It Works
- Continue to take as needed. Patients taking acute treatment more than 2 days/week are at risk for medication-overuse headache, especially if they have migraine

If It Doesn't Work
- Treat early in the attack – triptans are less likely to work after the headache becomes moderate or severe, regardless of cutaneous allodynia, which is a marker of central sensitization
- Address life style issues (e.g., stress, sleep hygiene), medication use issues (e.g., compliance, overuse), and other underlying medical conditions
- Change to higher dosage, another triptan, another administration route, or combination of other medications. Add preventive medication when needed
- For patients with partial response or reoccurrence, other rescue medications include NSAIDs (e.g., ketorolac, naproxen), antiemetic (e.g., prochlorperazine, metoclopramide), neuroleptics (e.g., haloperidol, chlorpromazine), ergots, antihistamine, or corticosteroid

Best Augmenting Combos for Partial Response or Treatment-Resistance
- NSAIDs or antiemetics/neuroleptics are often used to augment response

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Direct effect on systemic serotonin receptors (e.g., 5-HT_{1B} agonism on vasoconstriction)

Notable AEs
- Tingling, flushing, sensation of burning, vertigo, sensation of pressure, heaviness, nausea

Life-Threatening or Dangerous AEs
- Serotonin syndrome. Rare cardiac events including acute myocardial infarction and vasospasm have been reported with almotriptan. Life-threatening cardiac arrhythmias have been reported with other triptans

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- In most cases, only reassurance is needed. Lower dose, change to another

triptan, or use an alternative headache treatment

Best Augmenting Agents to Reduce AEs

- Treatment of nausea with antiemetics is acceptable. Other AEs decrease with time

DOSING AND USE

Usual Dosage Range

- 6.25–12.5 mg

Dosage Forms

- Tablets: 6.25 and 12.5 mg

How to Dose

- Most adult patients respond best at 12.5 mg oral dose and 6.25 mg for adolescents. Give 1 pill at the onset of an attack and repeat in 2 hours for a partial response or if the headache returns. Maximum 25 mg/day. The safety of treating > 4 migraine in a 30-day period has not been studied. Limit 10 days/month

Dosing Tips

- Treat early in attack

Overdose

- May cause hypertension, cardiovascular symptoms. Other possible symptoms include seizure, tremor, extremity erythema, cyanosis, or ataxia. For patients with angina, perform ECG and monitor for ischemia for at least 20 hours

Long-Term Use

- Monitor for cardiac risk factors with continued use

Habit Forming

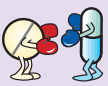
- No

How to Stop

- No need to taper. Patients who overuse triptans often experience withdrawal headaches lasting up to several days

Pharmacokinetics

- Half-life about 3–4 hours. T_{max} orally 1–4 hours. Bioavailability is 80%. Metabolized by monoamine oxidase (MAO)-A (27%; inactive indoleacetic acid metabolites) and CYP3A4/2D6 (12%; inactive GABA derivatives). 35% protein binding. Eliminated primarily by renal excretion (75%)



Drug Interactions

- MAO-A inhibitors may make it difficult for drug to be metabolized
- Minimal increase in concentration with CYP3A4 inhibitors – no need for dose adjustment

Do Not Use

- Patients with proven hypersensitivity
- Within 2 weeks of MAO-A inhibitors, or within 24 hours of ergot-containing medications such as dihydroergotamine
- History of stroke, transient ischemic attack, hemiplegic/basilar migraine, Wolff-Parkinson-White syndrome, peripheral vascular disease, ischemic heart disease, coronary artery vasospasm, ischemic bowel disease, and uncontrolled hypertension

SPECIAL POPULATIONS

Renal Impairment

- Start at 6.25 mg in those with moderate to severe renal impairment (CrCl < 30 mL/min). May be at increased cardiovascular risk. Avoid concomitant use of CYP3A4 inhibitors in patients with renal impairment

Hepatic Impairment

- Drug metabolism may be decreased. Do not use with severe hepatic impairment. Avoid concomitant use of CYP3A4 inhibitors in patients with hepatic impairment

Cardiac Impairment

- Do not use in patients with known cardiovascular or peripheral vascular disease. May have increased risk for vascular event

Elderly

- At an increased risk for cardiovascular incident. Most studies were done in patients