Perindopril

**CAS Number**: 107133-36-8  
**Molecular Formula**: C_{19}H_{32}N_{2}O_{5}  
**Molecular Weight**: 368.46 g/mol  
**Systematic (IUPAC)**: (2S,3aS,7aS)-1-[(2S)-2-[(2S)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-octahydro-1H-indole-2-carboxylic acid

**Type**: small molecule

**Description**  
Perindopril is a nonsulfhydryl prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class.
of medications. It is rapidly metabolized in the liver to perindoprilat, its active metabolite, following oral administration. Perindoprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Perindopril may be used to treat mild to moderate essential hypertension, mild to moderate congestive heart failure, and to reduce the cardiovascular risk of individuals with hypertension or post-myocardial infarction and stable coronary disease.

**Categories**
Antihypertensive Agents
Angiotensin-converting Enzyme Inhibitors

**Taxonomy**

**Kingdom** : Organic

**Classes**
Carboxylic Acids and Derivatives
Polypeptides

**Substructures**
Carboxylic Acids and Derivatives
Hydroxy Compounds
Acetates
Aliphatic and Aryl Amines
Amino Ketones
Pyrrolidines
**Pharmacology**

**Indication** : For the treatment of mild to moderate essential hypertension, mild to moderate congestive heart failure, and to reduce the cardiovascular risk of individuals with hypertension or post-myocardial infarction and stable coronary disease.

**Pharmacodynamics** : Perindopril is a nonsulfhydryl prodrug that is metabolized via first pass effect (62%) and systemic hydrolysis (38%) to perindoprilat, its active metabolite, following oral administration. Perindoprilat lowers blood pressure by antagonizing the effect of the RAAS. The RAAS is a homeostatic mechanism for regulating hemodynamics, water and electrolyte balance. During sympathetic stimulation or when renal blood pressure or blood flow is reduced, renin is released from the granular cells of the juxtaglomerular apparatus in the kidneys. In the blood stream, renin cleaves circulating angiotensinogen to ATI, which is subsequently cleaved to ATII by ACE. ATII increases blood pressure using a number of mechanisms. First, it stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone travels to the distal convoluted tubule (DCT) and collecting tubule of nephrons where it increases sodium and water reabsorption by increasing the number of sodium
channels and sodium-potassium ATPases on cell membranes. Second, ATII stimulates the secretion of vasopressin (also known as antidiuretic hormone or ADH) from the posterior pituitary gland. ADH stimulates further water reabsorption from the kidneys via insertion of aquaporin-2 channels on the apical surface of cells of the DCT and collecting tubules. Third, ATII increases blood pressure through direct arterial vasoconstriction. Stimulation of the Type 1 ATII receptor on vascular smooth muscle cells leads to a cascade of events resulting in myocyte contraction and vasoconstriction. In addition to these major effects, ATII induces the thirst response via stimulation of hypothalamic neurons. ACE inhibitors inhibit the rapid conversion of ATI to ATII and antagonize RAAS-induced increases in blood pressure. ACE (also known as kininase II) is also involved in the enzymatic deactivation of bradykinin, a vasodilator. Inhibiting the deactivation of bradykinin increases bradykinin levels and may sustain the effects of perindoprilat by causing increased vasodilation and decreased blood pressure.

**Mechanism of action**: There are two isoforms of ACE: the somatic isoform, which exists as a glycoprotein comprised of a single polypeptide chain of 1277; and the testicular isoform, which has a lower molecular mass and is thought to play a role in sperm maturation and binding of sperm to the oviduct epithelium. Somatic ACE has two functionally active domains, N and C, which arise from tandem gene duplication. Although the two domains have high sequence similarity, they play distinct physiological roles. The C-domain is predominantly involved in blood pressure regulation.
while the N-domain plays a role in hematopoietic stem cell differentiation and proliferation. ACE inhibitors bind to and inhibit the activity of both domains, but have much greater affinity for and inhibitory activity against the C-domain. Perindoprilat, the active metabolite of perindopril, competes with ATI for binding to ACE and inhibits and enzymatic proteolysis of ATI to ATII. Decreasing ATII levels in the body decreases blood pressure by inhibiting the pressor effects of ATII as described in the Pharmacology section above. Perindopril also causes an increase in plasma renin activity likely due to a loss of feedback inhibition mediated by ATII on the release of renin and/or stimulation of reflex mechanisms via baroreceptors.

**Absorption**: Rapidly absorbed with peak plasma concentrations occurring approximately 1 hour after oral administration. Bioavailability is 65-75%. Following absorption, perindopril is hydrolyzed to perindoprilat, which has an average bioavailability of 20%. The rate and extent of absorption is unaffected by food. However, food decreases the extent of biotransformation to peridoprilat and reduces its bioavailability by 35%.

**Protein binding**: Perindoprilat, 10-20% bound to plasma proteins

**Metabolism**: Extensively metabolized, with only 4-12% of the dose recovered in urine following oral administration. Six metabolites have been identified: perindoprilat, perindopril glucuronide, perindoprilat glucuronide, a perindopril lactam, and two perindoprilat lactams. Only perindoprilat is pharmacologically active.
Perindoprilat and perindoprilat glucuronide are the two main circulating metabolites.

**Route of elimination**: Perindopril is extensively metabolized following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine.

**Half life**: Perindopril, 1.2 hours; Perindoprilat, 30-120 hours. The long half life of perindoprilat is due to its slow dissociation from ACE binding sites.

**Clearance**
219 – 362 mL/min

**Toxicity**: The most likely symptom of overdose is severe hypotension. The most common adverse effects observed in controlled clinical trials include cough, digestive symptoms, fatigue, headache, and dizziness.

**Affected organisms**: Humans and other mammals

**Uses**
Perindopril is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. This medication is also used to prevent heart attacks in patients with a certain type of heart disease (stable coronary artery disease). Perindopril belongs to a class of drugs known as ACE inhibitors. It works by relaxing blood vessels so blood can flow more easily. OTHER This section contains uses of this drug that are not listed in the approved professional labeling for the drug but that
may be prescribed by your health care professional. Use this drug for a condition that is listed in this section only if it has been so prescribed by your health care professional. This medication may also be used to treat congestive heart failure and to help protect the kidneys from damage due to diabetes.

**How To Use?**

Take this medication by mouth, usually once or twice daily or as directed by your doctor. The dosage is based on your medical condition and response to therapy. For the treatment of high blood pressure, the manufacturer recommends taking no more than 16 milligrams per day. Do not take potassium supplements or salt substitutes containing potassium without talking to your doctor or pharmacist first. This medicine can raise your potassium levels, which rarely can cause serious side effects such as muscle weakness or a very slow heartbeat. Tell your doctor immediately if these effects occur. Take this medication regularly in order to get the most benefit from it. Remember to take it at the same time(s) each day. Do not skip doses or stop taking this medication unless directed by your doctor. It is important to continue taking this medication even if you feel well. Most people with high blood pressure do not feel sick. It may take up to several weeks before the full benefit of this drug takes effect. Inform your doctor if your condition worsens (e.g., your routine blood pressure readings increase).

**Drug Interactions**

See also How to Use section. Your healthcare professionals (e.g., doctor or pharmacist) may already be
aware of any possible drug interactions and may be monitoring you for it. Do not start, stop, or change the dosage of any medicine before checking with them first. Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: drugs affecting the bone marrow (e.g., azathioprine), lithium, nonsteroidal anti-inflammatory drugs-NSAIDs (e.g., celecoxib, ibuprofen, indomethacin), potassium-sparing "water pills" (diuretics such as amiloride, spironolactone, triamterene), products that may increase your potassium level (e.g., potassium supplements, salt substitutes, drospirenone), gold injections. A very serious reaction may occur if you are getting injections for bee/wasp sting allergy (desensitization) and are also taking perindopril. Make sure all your doctors know which medicines you are using. Check the labels on all your medicines (e.g., cough-and-cold products, diet aids, nonsteroidal anti-inflammatory drugs-NSAIDs for pain/fever reduction) because they may contain ingredients that could increase your blood pressure (e.g., pseudoephedrine, phenylephrine) or reduce the effect of this medication (e.g., ibuprofen, naproxen). Ask your pharmacist about the safe use of those products. Low-dose aspirin, as prescribed by your doctor for specific medical reasons such as heart attack or stroke prevention (usually at dosages of 81-325 milligrams per day) should be continued. Consult your doctor or pharmacist for more details. This document does not contain all possible interactions. Therefore, before using this product, tell your doctor or pharmacist of all the products you use. Keep a list of all your medications with you, and share the list with your doctor and pharmacist.
Why is this medication prescribed?
Perindopril is used alone or in combination with other medications to treat high blood pressure. Perindopril is in a class of medications called angiotensin-converting enzyme (ACE) inhibitors. It makes blood flow more smoothly by preventing the production of certain natural chemicals that tighten the blood vessels.

How should this medicine be used?
Perindopril comes as a tablet to take by mouth. It is usually taken once or twice a day. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take perindopril exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.
Your doctor may start you on a low dose of perindopril and gradually increase your dose.
Perindopril controls high blood pressure but does not cure it. Continue to take perindopril even if you feel well. Do not stop taking perindopril without talking to your doctor.

Other uses for this medicine
This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

What special precautions should I follow?
Before taking perindopril, tell your doctor and pharmacist if you are allergic to perindopril, benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril
(Prinivil, Zestril), moexipril (Univasc), quinapril (Accupril), ramipril (Altace), trandolapril (Mavik), or any other medications.
tell your doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking. Be sure to mention any of the following: cyclosporine (Neoral, Sandimmune), diuretics ('water pills'), heparin, indomethacin (Indocin), lithium (Eskalith, Lithobid), and potassium supplements (K-Dur, Klor-Con, others).
Your doctor may need to change the doses of your medications or monitor you carefully for side effects.
tell your doctor if you are on dialysis and if have or have ever had heart failure; lupus (SLE); scleroderma; diabetes; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, and/or lower legs (angioedema); or kidney or liver disease.
tell your doctor if you plan to become pregnant or are breast-feeding.
you should know that diarrhea, vomiting, not drinking enough fluids, and sweating a lot can cause a drop in blood pressure, which may cause lightheadedness and fainting.

**What special dietary instructions should I follow?**
Talk to your doctor before using salt substitutes containing potassium. If your doctor prescribes a low-salt or low-sodium diet, follow these directions carefully.

**What should I do if I forget a dose?**
Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the
missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

**What side effects can this medication cause?**
Perindopril may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:
- cough
- headache
- weakness
- dizziness
- diarrhea
- stomach pain
- upset stomach

Some side effects can be serious. The following symptoms are uncommon, but if you experience any of them, call your doctor immediately:
- swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- hoarseness
- difficulty swallowing or breathing
- lightheadedness
- fainting
- fever, sore throat, chills, and other signs of infection
- irregular or rapid heartbeats

Perindopril may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.

**What storage conditions are needed for this medicine?**
Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture.
(not in the bathroom). Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

**What other information should I know?**

Keep all appointments with your doctor.

Do not let anyone else take your medication. Ask your pharmacist any questions you have about refilling your prescription.

It is important for you to keep a written list of all of the prescription and nonprescription (over-the-counter) medicines you are taking, as well as any products such as vitamins, minerals, or other dietary supplements. You should bring this list with you each time you visit a doctor or if you are admitted to a hospital. It is also important information to carry with you in case of emergencies.

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