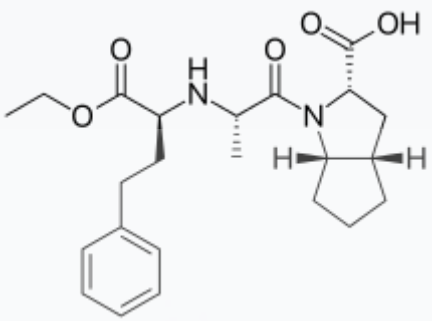
Ramipril

Ramipril	
	
Clinical data	
Trade names	Altace
AHFS/Drugs.com	Monograph
MedlinePlus	a692027
Pregnancy category	D
Routes of administration	Oral
ATC code	C09AA05 (WHO)
Legal status	
Legal status	UK: POM (Prescription only) US: ℞-only
Pharmacokinetic data	
Bioavailability	28%
Protein binding	73% (ramipril) 56% (ramiprilat)
Metabolism	Hepatic, to ramiprilat
Elimination half-life	2 to 4 hours

Excretion	Renal (60%) and fecal (40%)
Identifiers	
IUPAC name[show]	
CAS Number	87333-19-5 ✓
PubChem CID	5362129
IUPHAR/BPS	6339
DrugBank	DB00178 ✓
ChemSpider	4514937 ✓
UNII	L35JN3I7SJ
KEGG	D00421 ✓
ChEBI	CHEBI:8774 ✓
ChEMBL	CHEMBL1168 ✓
ECHA InfoCard	100.170.726
Chemical and physical data	
Formula	$C_{23}H_{32}N_2O_5$
Molar mass	416.511 g/mol
3D model (JSmol)	Interactive image
Melting point	109 °C (228 °F)
SMILES[show]	
InChI[show]	
(verify)	

Ramipril, sold under the brand name **Altace** among others, is an angiotensin-converting enzyme (ACE) inhibitor, used to treat high blood pressure (hypertension) and congestive heart failure. By inhibiting an enzyme, ACE inhibitors relax the muscles around small arteries (arterioles). The arterioles expand and allow blood to flow through more easily. This reduces blood pressure.

Medical uses

Indications for its use include:

- High blood pressure
- Congestive heart failure[1]
- Following heart attack in patients with clinical evidence of heart failure

- Susceptible patients over 55 years: prevention of heart attack, stroke, cardiovascular death, or need of revascularization procedures
- Kidney damage due to diabetes with protein in the urine (In low doses it is used as a prophylaxis for developing nephropathy and related secondary cardiovascular events.)[2]

Contraindications

Contraindications to its use include renovascular disease (impaired blood flow in the kidneys), severe renal impairment (especially in patients with one kidney or with bilateral renal artery stenosis), volume-depleted patients, a history of angioedema while on an ACE inhibitors, pregnancy, and hypotension.[citation needed]

Adverse effects

- Shakiness
- Dry cough
- Dizziness and light-headedness due to low blood pressure
- Fatigue, especially in the early stages
- Mouth dryness in the early stages
- Nausea
- Fainting
- Signs of infection (e.g., fever, chills, persistent sore throat)
- Chest pain
- Neutropenia (low white blood cells)
- Impotence (erectile dysfunction)[3]

Serious allergic reactions to this drug are unlikely, but immediate medical attention must be sought if they occur. Symptoms of a serious allergic reaction include, but are not limited to a rash or swelling of the face, mouth, tongue, or throat. In extreme cases, ramipril may lead to potentially fatal liver problems.

Mechanism of action

See also: Renin–angiotensin system

Ramipril 1.25-mg oral capsule,

letter codes and icons may differ

ACE inhibitors inhibit the actions of angiotensin converting enzyme (ACE), thereby lowering the production of angiotensin II and decreasing the breakdown of bradykinin. The decrease in angiotensin II results in relaxation of arteriole smooth muscle leading to a decrease in total peripheral resistance, reducing blood pressure as the blood is pumped through widened vessels. Its effect on bradykinin is responsible for the dry cough side effect.

Ramipril, a prodrug or precursor drug, is converted to the active metabolite ramiprilat by carboxylesterase 1.[4][5] Ramiprilat is mostly excreted by the kidneys. Its half-life is variable (3–16 hours), and is prolonged by heart and liver failure, as well as kidney failure.

US patent

The compound was protected by the U.S. Patent 5,061,722 which was assigned to the German pharmaceutical company Hoechst AG (since merged into Aventis) on 29 October 1991. The patent was scheduled to expire on 29 October 2008. On 11 September 2007, in an appeal by the Indian company Lupin Ltd., the United States Court of Appeals for the Federal Circuit reversed a district court trial verdict and found that Aventis's patent on ramipril was invalid for "obviousness", opening this drug to generic manufacturers.

Brand names

It is marketed as Prilace by Arrow Pharmaceuticals in Australia, Ramipro by Westfield Pharma in the Philippines, Tritace by Sanofi-Aventis in Italy and United States and Altace by King Pharmaceuticals in the United States, Novapril by Pharmanova in Ghana, Ramitens by PharmaSwiss, Ampril by Krka in Slovenia, Corpril by Cemelog-BRS in Hungary, Piramil and Prilinda by Hemofarm in Serbia, by Lek in Poland and by Novartis and Opsonin Pharma Limited as Ramace in Bangladesh, and in Canada as Altace (Sonfi) and Ramipril (Pharmascience).

Ramipril is marketed in India under the brand names Cardace, Zigpril, Ramistar, Odipril and Zorem . Ramipril is marketed in Myanmar under brand name Endpril .

Clinical trials

The Heart Outcomes and Prevention Evaluation trial[6][7] seemed to show ramipril possessed cardioprotective qualities which extended beyond its qualities as an antihypertensive. However, the trial and the interpretation of its results have been criticised.[8]

The AIRE trial[4][9] showed a 27% reduction in mortality for patients receiving ramipril for chronic heart failure following a myocardial infarction.

Ramipril was found to have similar results as telmisartan, an angiotensin II receptor blocker.[10]

References

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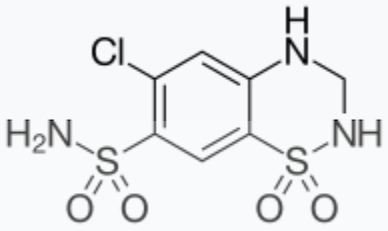
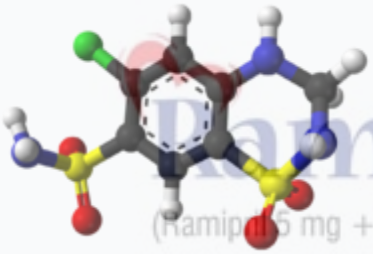
Hydrochlorothiazide

Hydrochlorothiazide





	Clinical data
Trade names	Apo-hydro, others
AHFS/Drugs.com	Monograph
MedlinePlus	a682571
License data	EU EMA: by INN
Pregnancy category	B (D if used to treat pregnancy-induced hypertension)
Routes of administration	Oral (capsules, tablets, oral solution)
ATC code	C03AA03 (WHO)
	Legal status
Legal status	In general: ℞ (Prescription only)
	Pharmacokinetic data
Bioavailability	Variable (~70% on average)

Metabolism	Not significant[1]
Elimination half-life	5.6–14.8 h
Excretion	Primarily kidney (>95% as unchanged drug)
Identifiers	
IUPAC name[show]	
CAS Number	58-93-5 ✓
PubChem CID	3639
IUPHAR/BPS	4836
DrugBank	DB00999 ✓
ChemSpider	3513 ✓
UNII	0J48LPH2TH
KEGG	D00340 ✓
ChEBI	CHEBI:5778 ✗
ChEMBL	CHEMBL435 ✓
ECHA InfoCard	100.000.367
Chemical and physical data	
Formula	$C_7H_8ClN_3O_4S_2$
Molar mass	297.74 g/mol
3D model (JSmol)	Interactive image
SMILES[show]	
InChI[show]	
✗✓ (what is this?) (verify)	

Hydrochlorothiazide (**HCTZ** or **HCT**) is a diuretic medication often used to treat high blood pressure and swelling due to fluid build up.[2] Other uses include diabetes insipidus, renal tubular acidosis, and to decrease the risk of kidney stones in those with high calcium level in the urine.[2] For high blood pressure it is often recommended as a first line treatment.[2][3] HCTZ is taken by mouth and may be combined with other blood pressure medications as a single pill to increase the effectiveness.[2]

Potential side effects include poor kidney function, electrolyte imbalances especially low blood potassium and less commonly low blood sodium, gout, high blood sugar, and feeling faint initially upon standing up.[2] While allergies to HCTZ are reported to occur more often in those with allergies

to sulfa drugs, this association is not well supported.[2] It may be used during pregnancy but is not a first line medication in this group.[2]

It is in the thiazide medication class and acts by decreasing the kidneys' ability to retain water.[2] This initially reduces blood volume, decreasing blood return to the heart and thus cardiac output.[4] Long term, however, it is believed to lower peripheral vascular resistance.[4]

Two companies, Merck and Ciba, state they discovered the medication which became commercially available in 1959.[5] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[6] In 2008 it was the second most commonly used blood pressure medication in the United States.[4] It is available as a generic drug[2] and is relatively affordable.[7]

Medical uses

Hydrochlorothiazide is frequently used for the treatment of hypertension, congestive heart failure, symptomatic edema, diabetes insipidus, renal tubular acidosis.[2] It is also used for the prevention of kidney stones in those who have high levels of calcium in their urine.[2]

Most of the research supporting the use of thiazide diuretics in hypertension was done using chlorthalidone, a different medication in the same class. Some more recent studies have suggested that chlorthalidone might be the more effective thiazide diuretic.[8]

It is also sometimes used for treatment of hypoparathyroidism,[9] hypercalciuria, Dent's disease, and Ménière's disease. For diabetes insipidus, the effect of thiazide diuretics is presumably mediated by a hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and increasing the urine osmolality.

Thiazides are also used in the treatment of osteoporosis. Thiazides decrease mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating osteoblast differentiation and bone mineral formation.[10]

It may be given together with other antihypertensive agents in fixed-dose combination preparations, such as in losartan/hydrochlorothiazide (see below).

Adverse effects

- Hypokalemia, or low blood levels of potassium are an occasional side effect. It can be usually prevented by potassium supplements or by combining hydrochlorothiazide with a potassium-sparing diuretic
- Other disturbances in the levels of serum electrolytes including hypomagnesemia (low magnesium), hyponatremia (low sodium), and hypercalcemia (high calcium)
- Hyperuricemia, high levels of uric acid in the blood
- Hyperglycemia, high blood sugar
- Hyperlipidemia, high cholesterol and triglycerides
- Headache
- Nausea/vomiting
- Photosensitivity
- Weight gain
- Gout
- Pancreatitis

These side effects increase with the dose of the medication and are most common at doses of greater than 25 mg per day.

Package inserts, based on case reports and observational studies, have reported that an allergy to a sulfa drug predisposes the patient to cross sensitivity to a thiazide diuretic. A 2005 review of the literature did not find support for this cross-sensitivity.[11]

Mechanism of action

Hydrochlorothiazide belongs to thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na^+) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral NaCl co-transporter by competing for the chloride site on the transporter. By impairing Na^+ transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.[12] Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.[13]

Society and culture

Co-Diovan (valsartan and HCTZ)

Two generic benazepril HCl 20 mg and HCTZ 25 mg oral tablets

Trade names

Hydrochlorothiazide is available as a generic drug under a large number of brand names, including Apo-Hydro, Aquazide, BPZide, Dichlotride, Esidrex, Hydrochlorot, Hydrodiuril, HydroSaluric, Hypothiazid, Microzide, Oretic and many others.

To reduce pill burden and in order to reduce side effects, hydrochlorothiazide is often used in fixed-dose combinations with many other classes of antihypertensive drugs such as:

- ACE inhibitors — e.g. Prinzide or Zestoretic (with lisinopril), Co-Renitec (with enalapril), Capozide (with captopril), Accuretic (with quinapril), Monopril HCT (with fosinopril), Lotensin HCT (with benazepril), etc.
- Angiotensin receptor blockers — e.g. Hyzaar (with losartan), Co-Diovan or Diovan HCT (with valsartan), Teveten Plus (with eprosartan), Avalide or CoAprovel (with irbesartan), Atacand HCT or Atacand Plus (with candesartan), etc.
- Beta blockers — e.g. Ziac or Lodoz (with bisoprolol), Nebilet Plus or Nebilet HCT (with nebivolol), Dutoprol or Lopressor HCT (with metoprolol), etc.
- Direct renin inhibitors — e.g. Co-Rasilez or Tekturna HCT (with aliskiren)
- Potassium sparing diuretics: Dyazide and Maxzide triamterene[14]

Sport

Use of hydrochlorothiazide is prohibited by the World Anti-Doping Agency for its ability to mask the use of performance-enhancing drugs.[15]

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