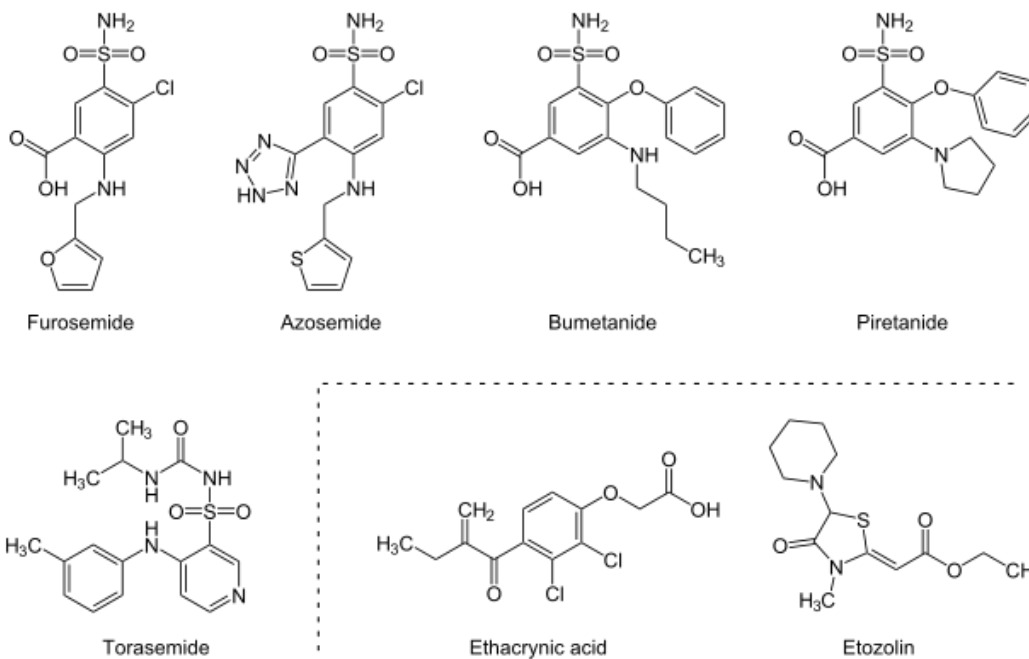


Loop Diuretics — Mechanism of Action and Adverse Effects

[See online here](#)

Loop diuretics are one of the important classes of diuretics. Furosemide is the most commonly used loop diuretics. Other loop diuretics used are bumetanide, torasemide, and ethacrynic acid. Loop diuretics are the most efficacious in causing diuresis in all the classes of diuretics. All the loop diuretics have the same mechanism of action, but different pharmacokinetic properties. They are used to treat/manage numerous diseases such as edema associated with CHF and liver cirrhosis. Diuretics most commonly cause electrolyte imbalance in the body on prolonged use.



Overview of Loop Diuretics

Diuretics are the drugs that increase the **urinary output** by increasing the **excretion of water and sodium** from the body. They are considered as the most important therapeutic agents in the treatment of numerous diseases, especially those associated with **volume overload** such as **edema**.

Loop diuretics (also called **high ceiling diuretics**) are one of the most commonly used classes of drug in clinical practice, and exert their action by **acting on the thick ascending loop of Henle**, hence called **“Loop diuretics”**.

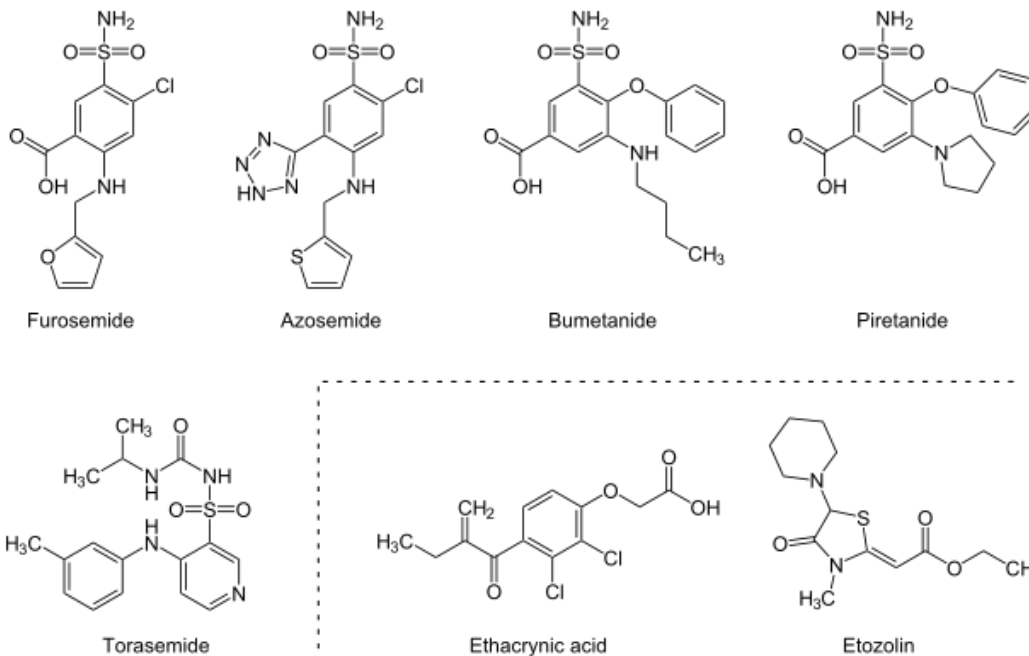
Among the loop diuretics, the most widely used drugs are:

Furosemide (Lasix): It is one of the most commonly used drugs in the treatment of **hypertension** and **edema** caused by **congestive heart failure (CHF)**.

Bumetanide (Bumex): It is indicated for the patients who are unresponsive to the furosemide (called furosemide resistance, occurs during prolonged therapy with furosemide) even at high doses. It is more bioavailable than furosemide and its absorption is not affected by the presence of food. Bumetanide is **40 times more potent** (rapid diuresis) than furosemide.

Torsemide (Demadex): It has a more prolonged diuretic action than furosemide, with less potassium loss. **No evidence of ototoxicity** with torsemide use.

Ethacrynic acid (Edecrin): Non-sulfa drug (other loop diuretics are sulfa drugs); It is associated with greater side effects than other loop diuretics and is the **most ototoxic loop diuretic**, therefore its use is limited now. It is used in patients hypersensitive to sulpha drugs.



[Image:](#) "Structure of the Loop Diuretics Furosemide, Azosemide, Bumetanide, Piretanide, Torasemide, Ethacrynic Acid and Etozolin" by NEUROtiker. License: Public Domain

Pharmacokinetics

All loop diuretics have the same mechanism of action; however, they differ from each in pharmacokinetics.

Route of Administration

They have different routes of administration such as oral and parenteral routes (intravenous/intramuscular).

Absorption

The **absorption** of loop diuretics is **rapid** with the peak serum concentration occurring

within 0.5 – 2 hours. There is variability in the absorption of loop diuretics. Bumetanide and torasemide (1 hour) are rapidly absorbed than the furosemide (60%).

Bioavailability

- Furosemide: 40 – 60% (average 50%)
- Bumetanide and torasemide: 80 – 100%

Thus, switching from intravenous to oral route in those with lesser bioavailability (such as furosemide) requires higher oral doses than the IV dose.

Drug Distribution and Half-Life

Furosemide and Bumetanide

- Half-life: About 1-2 hours
- Act rapidly through oral or intravenous route
- In oral route: Onset of effect occurs within 30-60 minutes and peaks at 30-120 minutes
- In IV route: Onset of effect is within minutes and peaks at about 20 minutes

Torasemide

- Half-life: About 3-4 hours
- Has a longer duration of action lasting about 6 hours
- Loop diuretics are **highly bound to albumin** and they are not filtered by glomerular filtration into the tubular lumen
- Loop diuretics are transported into the site of action by active secretion by the organic acid transport pump at the straight segment of the proximal tubule

Drug Elimination

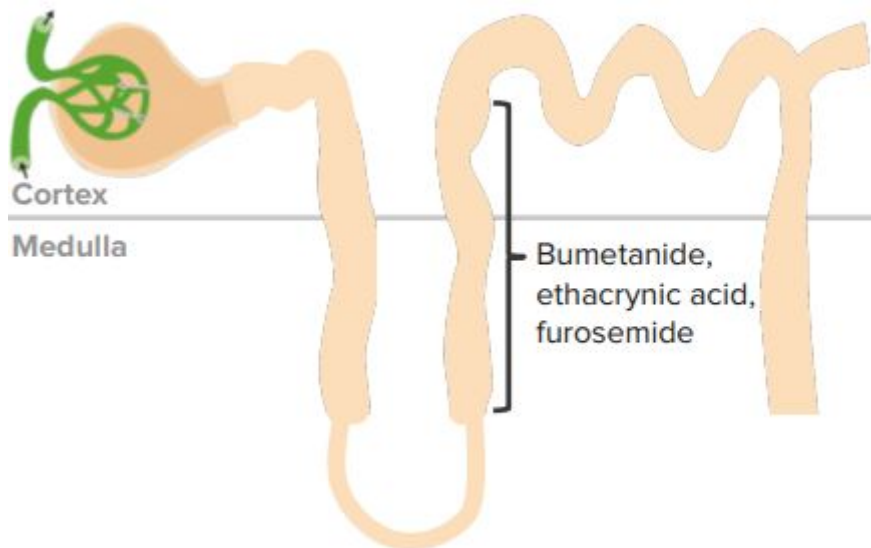
Furosemide

The route of elimination of furosemide is mainly renal with:

- **About half of furosemide is excreted unchanged**
- The remainder of the drug is conjugated with glucuronide in the **kidney** and then excreted.

Bumetanide and Torasemide

The route of elimination is mainly **liver**, in which they are metabolized by the **cytochrome p450 enzyme**.



"Loop Diuretics" Image created by Lecturio

Mechanism of Action

The thick ascending limb of Henle's loop is the site of action of loop diuretics.

This Henle's loop is characterized by being impermeable to water, although it powerfully and actively transports the **sodium, chloride and potassium** ions via the apical membrane **$\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter**. This makes the water in early distal tubular fluid hypotonic (about 100 mOsm/kg H_2O).

Sodium first binds to the cotransporter, promoting the binding of potassium and chloride ions, followed by binding with a second chloride ion.

Loop diuretic is a powerful inhibitor of $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the luminal membrane of the thick ascending limb of Henle's loop, which acts by competing with the chloride site (seemingly the second chloride binding site).

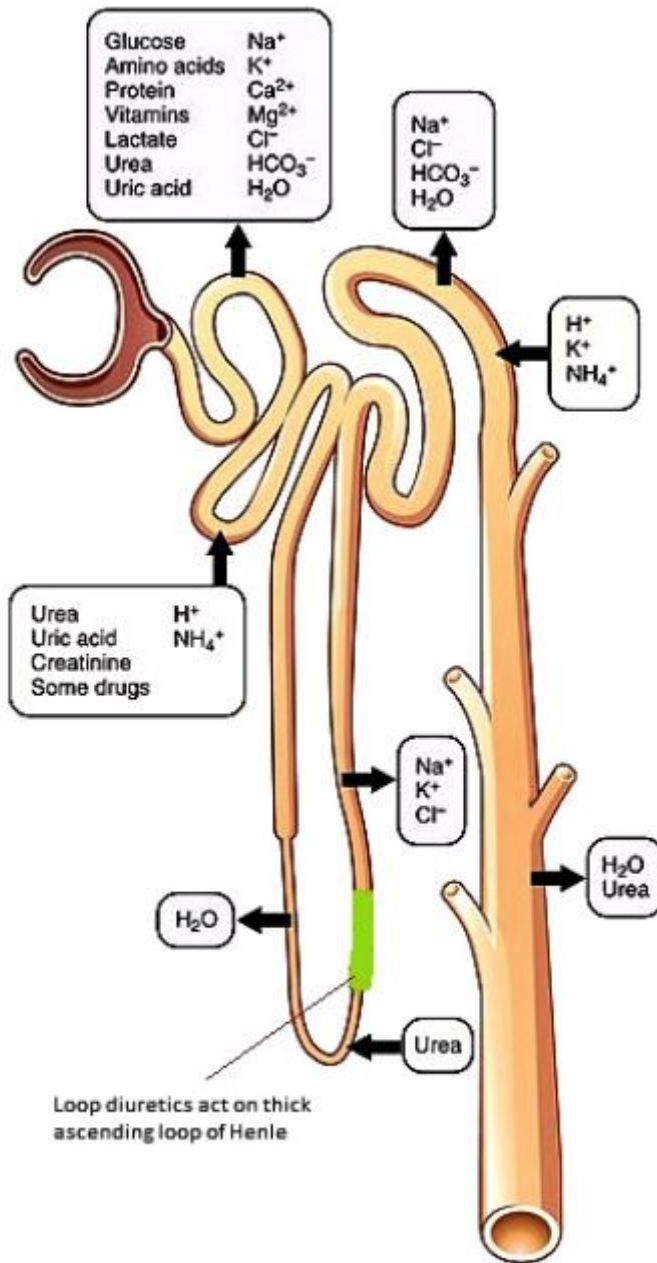


Image: "Site of action (highlighted in green) of loop diuretics in a nephron." by OpenStax College. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/) The image was altered.

Electrolyte	Reference range (mmol/L)
Sodium	136.00-146.00
Potassium	3.50-5.00
Chloride	98.00-107.00
Bicarbonate	22.00-29.00
Calcium	2.15-2.55

Table reference: [PhilSchatz](#)

This inhibitory effect of loop diuretics results in a decreased rate of sodium, chloride, potassium and other electrolytes reabsorption from these tubules into the medullary interstitium, thus inhibiting the formation of hypertonic medullary fluid. This leads to high osmotic pressure inside the renal tubules associated with a low osmolarity of the medullary interstitial fluid, which results in:

An increased sodium excretion (natriuresis) and increased excretion of other electrolytes,

such as chloride and potassium. Magnesium and calcium reabsorption is also inhibited because their absorption in the thick ascending limb depends mainly on the **positive lumen voltage gradient**, which is lost with loop diuretics usage.

A decreased in the reabsorption of water from the collecting ducts and descending loop of Henle into the hypotonic medullary fluid, due to the loss of the osmotic driving force of water into the hypotonic medullary interstitium → resulting in an increase in the urine output (diuresis) as great as 25 times of normal urine output.

Thus, loop diuretics aims to increase sodium excretion from the body with a subsequent increase in urine output resulting in a decrease in the extracellular fluid (ECF) volume in the clinical conditions that are associated with extracellular fluid (ECF) expansion, such as hypertension and [edema](#).

Indication

Loop Diuretics are used Mainly for Edematous Disorders

Congestive Heart Failure

The inability of the [heart](#) to pump [blood](#) may result in pulmonary congestion and peripheral edema. Loop diuretics can be used to remove excess fluid accumulation in acute heart failure or can be used to relieve the congestive symptoms and prevent further fluid accumulation.

Important: Loop diuretics are the **preferred drugs in CHF** over thiazides as thiazides are ineffective sometimes and used as maintenance in CHF.

Renal Failure

Chronic kidney disease (CKD) and **acute kidney insult (AKI)** are usually associated with volume overload because of the inability of the kidneys to excrete the salt and water.

Nephrotic Syndrome

Nephrotic syndromes are associated with **hypoalbuminemia**, which results in driving the water from vascular compartments into the interstitial space, therefore affected patients usually present with volume depletion.

Thus, diuretics should be used in nephrotic syndrome only in cases of severe edema or when there is no significant volume depletion.

Liver cirrhosis and ascitis

Liver cirrhosis releases vasodilators which stimulate the aldosterone release and salt and water retention and causes hypoalbuminemia. Loop diuretics are commonly used in chronic liver patients with ascitis.

Hypertension

Diuretics are commonly used in the treatment of hypertension by increasing [water and sodium loss](#). They can be used as the first-line treatment or as an adjunctive treatment with other hypotensive regimens.

Important: Thiazides are the preferred drugs in hypertension over loop diuretics;

furosemide is a **weak hypertensive** than thiazides.

Disorders of Calcium Metabolism

Loop diuretics increase the calcium excretion by the kidneys; therefore can be used in the **treatment of hypercalcemia**.

Cerebral Edema

Loop diuretic is usually **combined with mannitol** in the treatment of cerebral edema to decrease the intracranial pressure. It acts by inhibiting the local brain transport mechanisms, but not by its effect on salt and water excretion.

Adverse Effects

Acute Hypovolemia

Large doses of diuretics can lead to volume depletion, with the following subsequent consequences:

- Early symptoms: **Postural dizziness, easily fatigability and thirst**
- More severe cases can lead to decreased organ perfusion such as:
 - Brain: Confusion and drowsiness
 - Kidney: Acute kidney insult (elevation of blood urea nitrogen "BUN" and creatinine)
 - Heart: **Myocardial ischemia**
- Hypovolemic shock: It is associated with tachycardia, hypotension, cold extremities, cyanosis and oliguria

Electrolyte Disturbances

Hyponatremia

(Usually develops within the first **1-2 weeks** of therapy.)

In the presence of the **antidiuretic hormone (ADH)**, the high osmotic pressure in the medullary interstitium allows NaCl reabsorption through collecting ducts via the osmotic gradient between the lumen and hypertonic interstitium, resulting in the formation of concentrated urine. Loop diuretics inhibit this normal physiological process resulting in increased sodium and water excretion.

Diuretic-induced volume depletion stimulates **ADH secretion** from the posterior pituitary, but its effect on the kidneys is limited because of the impairment of lumen-medullary osmotic gradient.

Hyponatremia (serum sodium level of less than 135 mEq/L) occurs usually in the cases of **high water intake**, especially if associated with **impaired water excretion** as in elderly patients, and patients with renal diseases.

Important: Thiazides cause severe hyponatremia as compared to loop diuretics; this is due to their action on different sites at the nephron.

Hypokalemia

Loop diuretics cause potassium depletion by the following mechanisms:

Increased distal delivery of sodium to the collecting duct results in an increased tubular exchange of sodium for potassium with subsequently increased excretion of potassium resulting in **hypokalemia**.

Diuretic-induced volume depletion stimulates **mineralocorticoids (aldosterone)** release from the adrenal gland. **Aldosterone** increases the **rate of potassium secretion** by:

- a. Stimulating the activity of **Na/K ATPase** in the basolateral membrane, resulting in increased intracellular potassium concentration, which is then secreted into the tubular lumen.
- b. Directly increase the permeability of the luminal membrane to potassium.

Hypokalemia can be avoided by:

- Using potassium-sparing diuretics (e.g. **spironolactone**).
- Dietary supplementation of potassium.

Hypocalcemia and hypomagnesemia

Most of the reabsorbed potassium from the ascending limb of the loop of Henle via **Na-K-2Cl** cotransporters is recycled again back to the tubular lumen to drive further absorption of NaCl. Also, the reabsorbed chloride ions move back into the tubular lumen via chloride channels. The **cationic potassium and chloride ions** generate a net positive voltage gradient which allows the passive absorption of cations: **sodium, calcium, and magnesium**, via the **paracellular pathway between cells**.

Loop diuretics inhibit the Na reabsorption, and thus decrease the rate of potassium leakage into the tubular lumen and the generation of this positive voltage gradient, and thus decreasing the rate of absorption of calcium and magnesium and increasing the rate of their excretion.

Loop diuretics mnemonics: Loop all (loop diuretics loop most of the electrolytes)

Hyperuricemia

Loop diuretics can lead to hyperuricemia and gouty arthritis by two mechanisms:

Loop diuretics increase the **uric acid** level in the plasma by competing with the same **organic anion transporter** (both uric acid and loop diuretics are secreted by the same transporter on proximal tubule of nephron).

Both loop and thiazide diuretics decrease the uric acid excretion by increasing the reabsorption process of uric acid.

Hyperuricemia: Plasma uric acid level greater than 6.8 mg/dL at normal body temperature.

Acid-Base Disturbance (Metabolic alkalosis)

Loop diuretics can lead to metabolic alkalosis (elevation of the serum bicarbonate) by different mechanisms:

Diuretic-induced volume depletion results in the reduction of the extracellular fluid (ECF) resulting in concentrating the bicarbonate (HCO_3) in the plasma. This mild rise in HCO_3 is buffered by the release of H ions from cells and the uptake of HCO_3 into the bone, making this mechanism less effective.

Aldosterone released as a result of decreased extracellular fluid, increases the distal H ions secretion resulting in increased acid excretion (acidification) in distal nephrons, thereby increasing the new input of HCO₃ by kidneys into the venous blood.

Decreased **effective arterial blood volume** (EABV) decreases the renal perfusion and thus **glomerular filtration rate** (GFR) leading to the decreased filtration of HCO₃ and its excretion by the kidneys.

Hypersensitivity

Loop diuretics are sulfa drugs that might lead to **hypersensitivity reaction**, ranging from a rash to acute interstitial nephritis (rare).

Ototoxicity

Loop diuretics (especially ethacrynic acid and furosemide) can affect hearing temporarily or permanently based on the dose, duration, and route of administration. **Ethacrynic acid is the most ototoxic drug** in loop diuretics. It causes hearing loss by:

1. Morphological alterations in the cochlea and loss of outer hair cells.
2. Disturbances in endolymph potassium concentration.
3. Decrease in the electrical potentials of the cochlea.

Loop diuretics and other ototoxic drugs, such as **aminoglycosides**, should be used cautiously together.

Osteoporosis

Increase the risk of **osteoporosis** and incidence of fractures due to the diuretics-induced **hypocalcemia**.

Contraindications

- Hypersensitivity to sulpha drugs.
- Anuric patients.
- Patients with **hepatic coma**.
- Patients with severe electrolytes depletion.
- Ethacrynic acid is contraindicated in infants.

Precautions and Drug Interactions

- **Patients with gout:** Loop diuretics cause **hyperuricemia**.
- **Patients with prolonged Q-T interval:** Because diuretic-induced **hypokalemia** may increase the risk of **Torsades de points** in patients with prolonged Q-T interval.
- **Chronic liver patients with cirrhosis:** The volume depletion and electrolytes disturbances may precipitate **hepatic coma**.
- **Patients with significant kidney disease:** Patients may require adjustment of the doses.
- **NSAIDs intake:** NSAIDs decrease the diuretic action of loop diuretics due to the inhibition of PG (prostaglandins) synthesis. **PGE2 and PGI2** regulate the GFR and increase the NA, K and water excretion.
- **Digoxin and lithium intake:** Diuretics-induced hypokalemia may precipitate

digoxin and lithium toxicity.

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[JNC 8 Hypertension Guidelines](#) via ccmdweb.org

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Notes