BP 501T: MEDICINAL CHEMISTRY II
TOPIC: DIURETICS

Official Drugs:

	CLASS	DRUGS	Site and Mechanism of action	
1	Carbonic anhydrous Inhibitors (CAI)	**1.Acetazolamide**, 2.Methazolamide, 3. Dichlorphenamide	Collecting tube	Inhibition of reabsorption of bicarbonates
2	Thiazides	**4. Chlothiazide**. 5. Hydrochlorothiazide, 6. Hydroflumethiazide, 7. Cyclothiazide	Distal tube	Inhibition of Na+/Cl- transport
3	loop Diuretics	**8. Furosemide**. 9. Butamide, 10. Ethacrynic acid	Thick ascending limp, loop of henle	Inhibition of Na+/K+/Cl- cotransport
4	K+Sparing Diuretics	11. Spironolactone, 12. Triamterene, 13. Amiloride	Distal tube, collecting duct	Inhibition of Na reabsorption and K+ secretion
5	Osmotic Diuretics	14. Mannitol	Proximal tube, collecting duct Loop of henle	Inhibition of Na+ and water reabsorption

Diuretics are drugs that reduce the volume of extracellular fluid (ECF), and increase the volume of urine excreted by kidneys. Consequently, diuretics are used in the treatment of hypertension, edema associated with congestive heart failure (CHF), acute pulmonary edema, diabetes insipidus, acute and chronic renal failure and the nephritic syndrome. The formation of urine from the blood consists of glomerular filtration and

selective tubular reabsorption and secretion. The normal glomerulus filtration rate (GFR) is about 100 ml/min, out of which, 99ml of the fluid is returned to the blood, and only 1% is excreted as urine.

Diuretics may increase the rate of urine formation by
1. Increasing Glomerular filtration, and
2. Decreasing tubular reabsorption

1. ACETAZOLAMIDE (Diamox)

CATEGORY: Carbonic anhydrous inhibitor (CAI)

NOMENCLATURE:

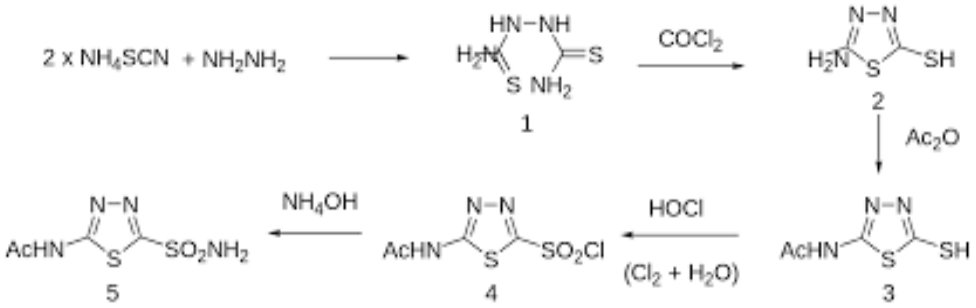
5-acetamido-1, 3, 4-thiazol-2-sulfonamide

N-[5-(aminosulfonyl)-1, 3, 4-thiadiazol-2yl] acetamide

PROPERTIES: White to faintly yellowish white, crystalline, odorless powder. Very slightly soluble in water; sparingly soluble in hot water; slightly soluble in ethanol; it is soluble in dilute solutions of alkali hydroxides; practically insoluble in chloroform and ether

SYNTHESIS:

5-amino-1, 3, 4-thaidiazole-2-thiol (2) is prepared by the treatment of hydrazine derivative with phosgene. Compound (1) is acetylated with acetic anhydride leads to 5 –acetamido-1, 3, 4-thiadiazole-2-thiol (3), which by oxidation, gives Sulfonyl chloride (4); followed by ammonolysis with ammonia gives Acetazolamide (5)



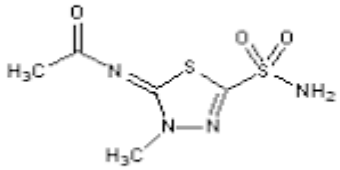
MOA: Acetazolamide is a prototypical, weak diuretic agent, acts by selectively inhibiting carbonic anhydrous enzyme in the membrane and cytoplasm of the epithelial cells. This enzyme is responsible for catalytic reversible hydration of carbon dioxide and water to form carbonic acid (H_2CO_3). The site of action is proximal convoluted tube (PCT).

PHARMACOKINETICS: Given orally, it is well absorbed from the GI Tract and widely distributed throughout the body. It is 93% protein bound, peak plasma concentration are reached within 2 hours. Its half-life is 5 hours. Duration of action ranges from 8-12 hrs

USES: Used in the treatment of open angular glaucoma, it is also used in certain types of epilepsy such as absence, generalized tonic-colonic and focal seizures. It is employed in acute mountain sickness and useful in prophylaxis of hyperkalemia.
DOSE 500 mg (initially); subsequent doses, 250 mg every 6 hours.
OFFICIAL PREPARATIONS: Acetazolamide tablet 125 and 250 mg; 500 mg SR-capsule; 500 mg powder for injection (sodium salt) can be given parenterally.

2. METHAZOLAMIDE (**Glauctabs**; **Neptazane**,)

CATEGORY: Carbonic anhydrase inhibitors diuretic
NOMENCLATURE: N-(4methyl2-sulfonyl1, 3, 4-thiadiazol5yliden) acetamide



PROPERTIES: White to yellowish-white; odorless, crystalline powder. It is almost insoluble in water, ether and chloroform; soluble in methanol; slightly soluble in ethanol. It is soluble in solutions of alkali hydroxides
MOA: Its action similar to Acetazolamide diuretics. Invitro studies shown that Methazolamide to be more potent CAI than the prototype drug acetazolamide
PHARMACOKINETICS:
It is well absorbed orally; bioavailability is about; it has a long duration of action (48-72 hours). It is extensively bound to carbonic anhydrase enzyme in the erythrocytes.
USES: It is used to reduce elevated intraocular pressure in open angle glaucoma or ocular hypertension
DOSE: 25-50 mg daily
PREPARATIONS: Methazolamide Tablets
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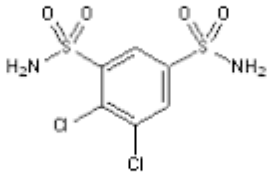
3. DICHLORPHENAMIDE (Daranid)

CATEGORY: Carbonic anhydrase Inhibitors diuretic
NOMENCLATURE: 4, 5 -dichlorobenzene 1, 3-disulphonamide

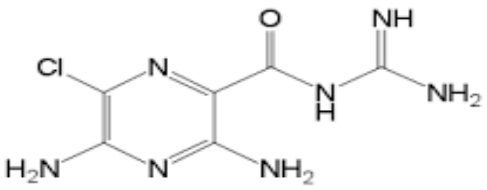


PROPERTIES: White to yellowish white, odorless, crystalline powder. It is almost insoluble in water, ether and chloroform; soluble in methanol; slightly soluble in ethanol. It is soluble in solutions of alkali hydroxides
MP: Melts between at 236.5 and 240^0
MOA: Its action similar to acetazolamide Carbonic anhydrase inhibitors.
PHARMACOKINETICS:
It is well absorbed orally; it has a long duration of action (48-72 hours).
USES: It is used to reduce intraocular pressure and useful in the treatment of primary and the acute phase of secondary glaucoma
DOSE: 50 mg daily
PREPARATIONS: Dichlorphenamide Tablets

4. AMILORIDE (Midamor)

CATEGORY: Potassium Sparing Diuretics

NOMENCLATURE: N-amidino-3, 5-diamino-6-chloropyrazin2-carboxamide



PROPERTIES: A pale yellow to greenish yellow, odorless Powder. It is slightly soluble in water. It is insoluble in acetone, in chloroform, in ether, in ethylacetate. Freely soluble in dimethylsufoxide; sparingly soluble in methanol

MP: Melts at about 240^0.

MOA: Its action on the distal renal tube (DRT), it increases the excretion of sodium and decrease the excretion of potassium.

PHARMACOKINETICS: It is incompletely absorbed in GI Tract; bioavailability is about 50% and is reduced in the presence of food; it has plasma half-life is about 6-9 hours.

USES: It is a week diuretic, mainly used in adjunction with thiazide and loop diuretics, used in refractory edema associated with hepatic cirrhosis and in the treatment of hypertension.

DOSE: 5-10 mg daily (Maximum 20 mg)

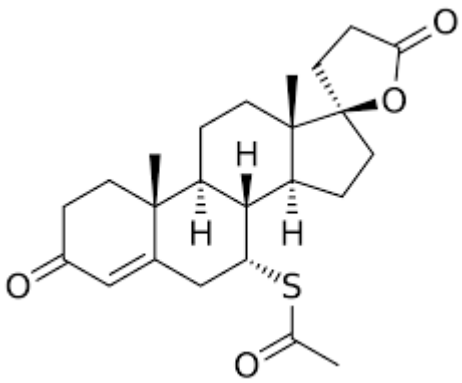
PREPARATIONS: Amiloride hydrochloride Tablets

Co-Amiloride Tablets, Oral Suspension BP (Compounded preparation of Amiloride Hcl and Hydrochlorothiazide as 1part to 10 parts)

5. SPIRONOLACTONE (Aldactone, Spirolactone)

CATEGORY: Potassium Sparing Diuretics

NOMENCLATURE: 7- alpha acetylthio 3-oxo 17- alpha pregn4ene 21, 17-beta-carbolactone



PROPERTIES: A white or yellowish white powder, practically insoluble in water; soluble in alcohol. It exhibit polymorphism. It should be protected from light. Stable in air; melts between 198 and 207 ^{0} with decomposition

MOA: Spironolactone is a synthetic C_{17} lactone steroid with structural similarity to aldosterone (a mineralocorticoid). It acts by competitively antagonizing the hormone aldosterone on the distal renal tubule (DRT), blocking Na^{+} exchange for K^{+} and H^{+} ions, resulting in retention of K^{+} and increased secretion of water and sodium.

PHARMACOKINETICS: It is rapidly absorbed from G I Tract and extensively undergoes biotransformation in the liver, forming an active metabolite *Canrenone*, which is

responsible for about 80% of activity. This metabolite bound to plasma proteins about 98% and half-life is about 10-34 hours. Potassium sparing diuretics should not be taken by diabetic patients, as they can cause life-threatening hyperkalemia. High doses of Spiranolactone 100 mg or above daily cause gynecomastia as well as loss of libido and impotence in man.

USES: Used in the treatment of edema associated with chronic CHF, Cirrhosis and nephritic syndrome. It is also used in the treatment of hypertension and in hirsutism. Its efficiency is enhanced when administrated with Thiazide or loop diuretic. It is indicated for diagnosis and short or long term management of primary hyperaldosteronism

DOSE: Orally, 25-200 mg/ day in divided doses

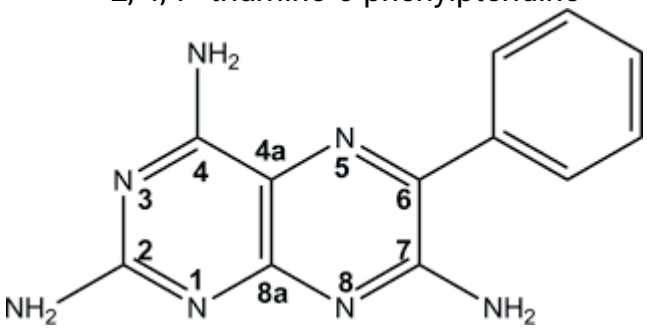
PREPARATIONS:

Spiranolactone available as 25 mg 50 mg and 100 mg tablets; it can be used in combination with hydrochlorothiazide (**ALDACTAZIDE**) in 1:1 ratio (as 25 mg and 25 mg)

6. TRIAMTERENE (Dyrenium, Dytac)

CATEGORY: Diuretic-potassium sparing

NOMENCLATURE: 6-phenyl-2, 4, 7-pteridinetriamine
2, 4, 7- triamino-6-phenylpteridine



PROPERTIES:

Yellow, odorless, crystalline powder; stable in light and temperature

Practically insoluble in, ether, soluble in formic acid; slightly soluble in water (1 in 1000), ethanol (1 in 3000), chloroform (1in 4000)

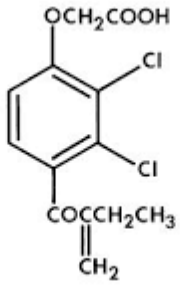
MOA: Triamterene is a pteridine derivative. It is a sodium channel blocker. It has direct action on the distal renal tubule of the nephron. It inhibits the reabsorption of sodium in exchange of potassium and hydrogen ions. The effect is unrelated to the level of aldosterone secretion.

PHARMACOKINETICS: after oral administration of Triamterene, 30-70% absorbed, and 50-67% bound to plasma protein. The diuretic effect begins within 2 hours, reaches peak in 6-8 hours, and persist for 12-16 hours. It is metabolized in the liver as hydroxy-triamterene sulfate, an active metabolite.

USES: Used in the treatment of edema associated with CHF, cirrhosis and in nephritic syndrome. Indicated in steroid-induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism
DOSE 100 to 200 mg
OFFICIAL PREPARATIONS: Triamterene 50mg Tablets. It can also be given in combination with hydrochlorothiazide 25 mg (Dyazide)

7. ETHACRYNICACID (Edecrin)

CATEGORY: Loop or high ceiling Diuretics
NOMENCLATURE: 2, 3-dichloro 4-(2-methylenebutyryl) phenoxy acetic acid



PROPERTIES: white crystalline powder; odorless, and has a bitter taste relatively stable in light and at room temperature; non hygroscopic, melts between 121- 125^0 C
It is very slightly soluble in water; it dissolves in ammonia and in dilute aqueous alkali hydroxides and carbonates solutions
MOA: It is an aryloxyacetic acid derivative, a potent short acting diuretic as similar to Furosemide.
PHARMACOKINETICS: It is well absorbed orally; plasma half-life is about 1hr; it has duration of action (6-8 hours).
USES: It is used in edema with Cardiac insufficiency. Cirrhosis of the liver and renal disease, including nephritic syndrome
DOSE: orally 50- 150 mg daily
Parenterally 50mg, may be increased to 100mg (if necessary)
PREPARATIONS: Ethacrynic acid tablets IP
Ethacrynic acid (sodium salt) injection BP

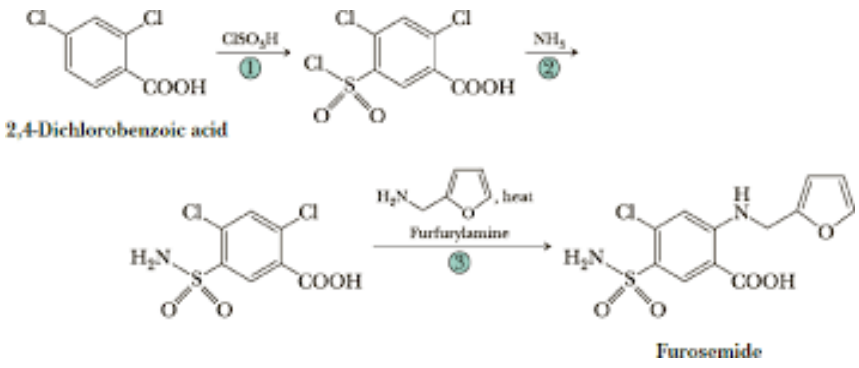
8. FUROSEMIDE (Frusid; Lasix)

CATEGORY: Loop or High ceiling diuretics

NOMENCLATURE: 5-(aminosulfonyl) 4-chloro 2-([2-furanylmethyl) amino] benzoic acid
4-chloro N-furfuryl 5-sulfamoylanthranilic acid

PROPERTIES: Slightly yellow, odorless, crystalline powder; practically insoluble in water and in chloroform; freely soluble in acetone; soluble in methanol; sparingly soluble in alcohol and slightly soluble in ether.

SYNTHESIS: Reaction with 2, 4-dichorobenzoic acid and chlorosulfonic acid gives di-chloro Sulfonyl derivative, by reaction with ammonia further converted to corresponding amide, and finally reaction with furfurylamine at 130^0 c for 4 hrs, gives Furosemide



MOA: it is a diuretic drug chemically related to sulphonamide. Its action is primarily by inhibiting active reabsorption of chloride ions in thick ascending limb of the loop of henle.

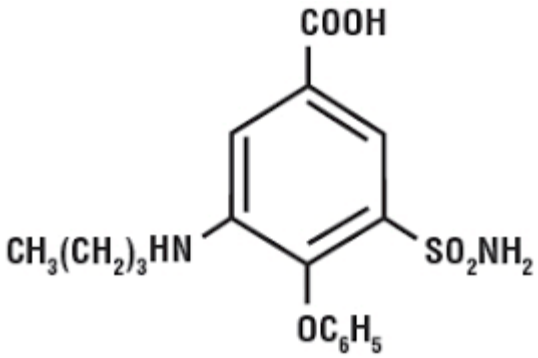
PHARMACOKINETICS: It is rapidly absorbed orally; bioavailability is about 60-70%.; it has plasma half-life about 2hrs. The diuretic effect persists for 6-8hrs

USES: Furosemide is a potent diuretic with rapid onset of action. It is most widely used

in acute pulmonary edema associated with CHF; acute renal failure and in hypertensive crisis
DOSE: For edema orally 20-80 mg as single dose or by parenterally
PREPARATIONS: Furosemide Tablets IP
Furosemide injection (sodium salt) IP, BP

9. BUMETANIDE (Bumex; Burinex)

CATEGORY: Loop or high-ceiling Diuretic
NOMENCLATURE: 3-butylamino 4-phenoxy 5-sulfonyl benzoic acid



PROPERTIES: white or almost white crystalline powder; practically insoluble in water; soluble in acetone and in alcohol; slightly soluble in dichloro methane. It exhibit polymorphism. It should be stored in air tight container
MOA: Its action similar to furosemide. It is more potent than furosemide with rapidly onset of action, 3-5 minutes parenterally; duration of action is 3.5-4 hrs
PHARMACOKINETICS:
It is well absorbed orally; bioavailability is about 85-90%; it has more extensive biotransformation in humans.
USES: It is used in the treatment of edema with heart failure. Also used in renal and hepatic disorder; it has also been used in hypertension.
DOSE: For Hypertension 0.5-2mg mg daily

For Edema: 1-2 mg daily

PREPARATIONS: Bumetanide injection BP
Bumetanide oral solution BP,
Bumetanide Tablets BP

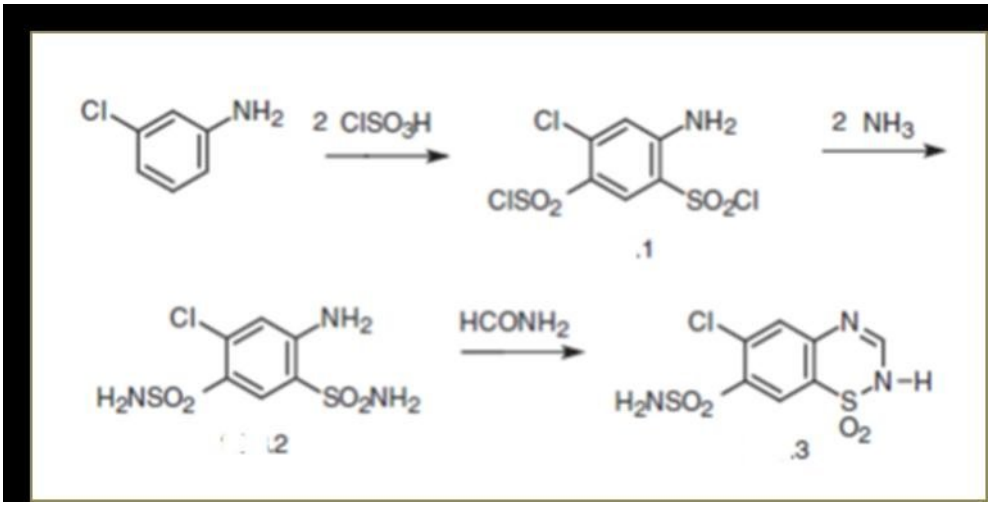
10. CHLORTHIAZIDE (Diuril)

CATEGORY: Thiazide Diuretic

NOMENCLATURE: 6-chloro 2H-1, 2, 4-benzothiadiazine 7-sulphonamide 1, 1-dioxide

PROPERTIES: white almost white crystalline powder. Slightly soluble in water

SYNTHESIS: 4, 6- sulfonolchloride 3-chloroaniline is prepared by the reaction between 3-chloroaniline and chlorosulfonic acid, further reaction with ammonia gives 4, 6-disufonylamido 3-chloroaniline, finally heating with formamide leads to the formation of chlothiazide.

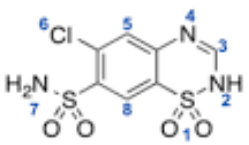


MOA: Its action similar to thiazide diuretics.

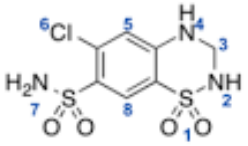
PHARMACOKINETICS:
It is incompletely and variably absorbed orally; the plasma half-life about 45-120 minutes; duration of action 6-12hrs
It is excreted as unchanged in urine.
USES: It is most widely used in the treatment of edema associated with mild to moderate CHF, cirrhosis of the liver. Diuril is 10 times less potent than Esidrex (hydrochlorothiazide)
PREPARATIONS: Chlothiazide Tablets, Oral suspension and injection (sodium salt)
Dose: 200-500mg antihypertensive
500-1gram Diuretics

11. HYDROCHLOTHIAZIDE (Esidrex)

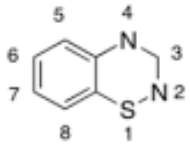
CATEGORY: Thiazide Diuretic
NOMENCLATURE:
6-chloro 2, 3-dihydro *2H*-1, 2, 4-benzothiadiazine 7-sulphonamide 1, 1-dioxide



Chlorothiazide



Hydrochlorothiazide

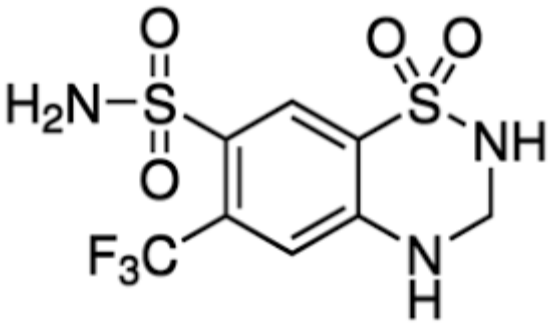


PROPERTIES: white almost white crystalline powder. It is very slightly soluble in water, dissolves in dilute alkali hydroxide solution
MOA: Its action similar to thiazide diuretics.
PHARMACOKINETICS: It is rapidly absorbed orally; the plasma half-life about 5-15Hrs.
It is excreted as unchanged in urine.
USES: It is most widely used in the treatment of hypertension and edema

DOSE: 25—100 mg daily;
25- 50mg daily in single or divided dose for hypertension
PREPARATIONS: Hydrochlorothiazide Tablets IP, BP
Co-amilozide Tablets & Oral solution BP with Amiloride (as 1:10 ratio)

12. HYDROFLUMETHIAZIDE (Diucardin, Saluron)

CATEGORY: Thiazide diuretics
NOMENCLATURE:
3, 4-dihydro 6-tryfluoromethyl *2H*-1, 2, 4-benzothiadiazine 7-sulphonamide 1, 1-dioxide

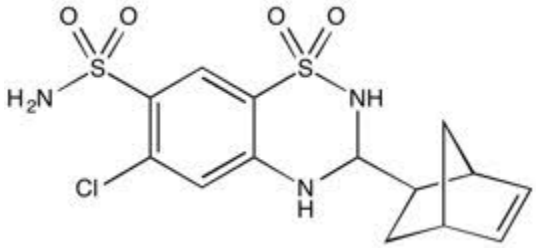


PROPERTIES: White or almost white glistering crystals or crystalline powder, practically insoluble in water.
MOA: Its action similar to other thiazide diuretics.
PHARMACOKINETICS:
It is incompletely but rapidly absorbed orally;
Bioavailability is about; it has a long duration of action (18-24 hours). It is extensively bound to carbonic anhydrase enzyme in the erythrocytes.

USES: It is most widely used in edema and hypertension
DOSE: For diuretic: 25-200 mg daily
For hypertension: 25-50mg daily
PREPARATIONS: Hydroflumethiazide Tablets BP

13. CYCLOTHIAZIDE (Anhydron)

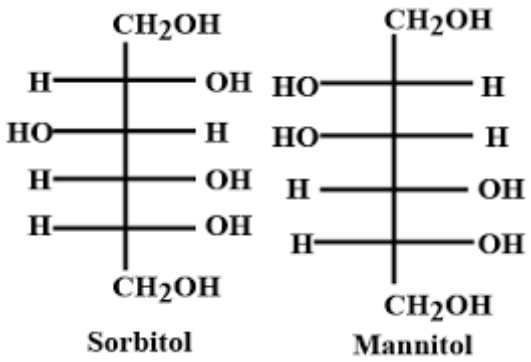
CATEGORY: Thiazide Diuretics
NOMENCLATURE: 6-chloro 3-cyclopentylmethyl 3, 4-dihydro-1, 2, 4-benzothiadiazine 7-sulphonamide 1, 1-dioxide



PROPERTIES: white to nearly white, practically odorless powder.
Solubility: soluble 1 gram in 70ml alcohol or 30 ml methanol; practically insoluble in water, chloroform or ether.
MOA: Its action is inhibits Na+/Cl- reabsorption from distal convoluted tubes on the kidneys.
PHARMACOKINETICS:
It is well absorbed orally; bioavailability is about; it has a long duration of action (18-24 hours). It is extensively bound to carbonic anhydrase enzyme in the erythrocytes.
USES: It is used as adjunctive therapy in edema associated with CHF, hepatic cirrhosis and estrogen therapy. it is also used in the management of hypertension
DOSE: Usual dose range 1-2mg daily
PREPARATIONS: Cyclothiazide Tablets

14. MANNITOL (Osmitrol)

CATEGORY: Osmotic Diuretics
NOMENCLATURE: D-Mannitol



PROPERTIES: white crystalline powder, or free flowing granules; freely soluble in water. The injection should be stored in temperature between 20- 30^0 C to avoid deposition of crystals
MOA: Its action is to mobilize fluid.by increasing osmotic pressure of tubular fluid
PHARMACOKINETICS: It is only small amount of drug are absorbed in GI Tract;
USES: It is mainly used as infusion to preserve renal function in acute renal failure and to reduce elevated intracranial and intraocular pressure.
DOSE: 50-200 g daily as infusion
PREPARATIONS: Mannitol injection IP
Mannitol intravenous infusion BP