

APO- FRUSEMIDE

Frusemide 40 mg tablets

Presentation

APO-FRUSEMIDE 40mg tablets are white, round, flat faced bevel edged tablets. 8.0mm diameter identified AF over breakline over 40 on one side. Each tablet contains 40mg of frusemide and typically weighs 184mg.

Uses

Actions

Frusemide is a loop diuretic with a rapid action. Frusemide appears to inhibit the reabsorption of electrolytes in the distal and proximal tubules and primarily in the ascending limb of the loop of Henle. Excretion of sodium, potassium, calcium and chloride ions and water is enhanced. Frusemide has no effect on carbonic anhydrase.

Pharmacokinetics

Frusemide is rapidly absorbed from the gastrointestinal tract with absorption rates of 60 to 70% in healthy subjects and 43 to 46% in patients with end stage renal failure. The onset of diuresis following oral administration occurs within one hour. Peak plasma levels are reached within one to two hours and the diuretic effect of frusemide lasts between six and eight hours.

Frusemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 µg/mL are 91 to 99% bound in healthy individuals. The unbound fractions average from 2.3 to 4.1% at therapeutic concentrations.

Frusemide glucuronide is the major known metabolite of frusemide in humans.

Approximately 66% of ingested frusemide is excreted in the urine by glomerular filtration and proximal tubular secretion, the remainder is secreted in the faeces.

Frusemide has a biphasic half-life in the plasma ranging up to 100 minute which is prolonged by renal and hepatic insufficiency and in newborn infants.

Indications

Oedema:

APO-FRUSEMIDE tablets are indicated for the treatment of oedema associated with congestive heart failure, pulmonary, renal and hepatic disorder in adults, infants and children.

APO-FRUSEMIDE is particularly useful when an agent with greater diuretic potential than of those commonly employed is desired.

Hypertension:

APO-FRUSEMIDE may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who can not be adequately controlled with thiazides will probably also not be adequately controlled with APO-FRUSEMIDE alone.

Dosage and Administration

Therapy should be individualised according to patient's response. Therapy should be titrated to gain maximal therapeutic response with the minimum dose possible to maintain the diuretic response.

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Treatment of oedema

Adults:

The usual initial dose is 20 to 80mg daily given as a single dose. If the diuretic response is not satisfactory, the dose should be increased by increments of 20 to 40mg, not sooner than 6 to 8 hours after the previous dose, until the desired diuretic effect is obtained. Once the individual dose is established, it should be administered once or twice daily. The dose of APO-FRUSEMIDE can be carefully titrated up to 400 mg/day (except in the case of advanced renal failure) in patients with severe clinical oedematous status. Giving APO-FRUSEMIDE on 2 to 4 consecutive days each week may be the most efficient and safe way of mobilising the oedema. When doses in excess of 80mg per day are given for prolonged periods careful clinical laboratory observations are advisable.

Infants and children:

The usual initial is 2mg/kg body weight administered as a single dose. The dose may be increased by 1 to 2 mg/kg no sooner than 6 to 8 hours after the previous dose if the diuretic response is not satisfactory. Doses should not exceed 6mg/kg body weight. For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

Hypertension

The usual initial dose is 80mg, usually divided into 40mg twice daily, either alone or in conjunction with other antihypertensive agents. The dosage of other agents should be reduced by at least 50% when used together with APO-FRUSEMIDE to prevent an excessive drop in blood pressure. Due to the potentiating effect of APO-FRUSEMIDE a further reduction in dosage or even discontinuation of other antihypertensive drugs may be indicated.

Contraindications

APO-FRUSEMIDE is contraindicated in patients with:

- Known hypersensitivity to frusemide or sulphonamides
- Complete renal shutdown. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease discontinue frusemide
- Severe hypokalaemia, hyponatraemia, hypovolaemia or hypotension until serum electrolytes, fluid balance and blood pressure have been restored to normal.
- Hepatic coma and conditions producing electrolyte depletion until underlying conditions have been corrected or ameliorated.
- Newborns presenting jaundice.
- Infants with conditions which might induce hyperbilirubinaemia or kernicterus.

Warnings and Precautions

Excessive diuresis may result in dehydration and reduction in blood volume with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Excessive loss of potassium in patients receiving cardiac glycosides may precipitate digitalis toxicity.

Tinnitus and reversible and irreversible hearing impairment have been reported. From these reports, frusemide ototoxicity is associated with severe renal impairment, doses exceeding the recommended dose several times, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid or other ototoxic medicines.

Initiation of therapy and APO-FRUSEMIDE in patients with hepatic cirrhosis and ascites should be carried out in hospital. Sudden alterations of fluid and electrolyte balance in

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patients with cirrhosis may precipitate hepatic coma, therefore strict observation is necessary during the period of diuresis.

Caution should be exercised when administering curare or its derivatives to patients undergoing frusemide therapy. It is advisable to discontinue frusemide for one week prior to elective surgery.

Strict restriction of sodium intake is not advisable in patients receiving frusemide as this is conducive to hyponatraemia and hypokalaemia.

In patients with impairment of micturition or prostatic hypertrophy frusemide should be used with care.

As with any effective diuretic, electrolyte depletion may occur during therapy with APO-FRUSEMIDE, especially in patients receiving higher doses and a restricted salt intake. Periodic determinations of serum electrolytes to detect possible imbalance should be performed at regular intervals, as well as creatinine, blood urea and CO₂ content. All patients receiving APO-FRUSEMIDE should be observed for signs of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemic alkalosis and hypokalaemia. When a patient is vomiting excessively or receiving parenteral fluids serum and urine electrolyte determinations are particularly important. Warning signs include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia and gastrointestinal disturbances such as nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of APO-FRUSEMIDE.

During long-term therapy, a high potassium diet is recommended and potassium supplements may be required. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids or with infants and children. Potassium supplementation, reducing the dose or discontinuation of frusemide may be required.

Periodic checks on urine and blood glucose should be made in diabetics and patients suspected of latent diabetes when receiving APO-FRUSEMIDE. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and 2-hour post prandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

APO-FRUSEMIDE may lower calcium levels and rare cases of tetany have been reported. Periodic serum calcium levels should therefore be obtained.

APO-FRUSEMIDE administered during the first weeks of life to premature infants with respiratory distress syndrome, may increase the risk of persistence of Botallo's duct.

Reversible elevations of blood urea may be observed in association with dehydration, which should particularly be avoided in patients with renal insufficiency.

Frusemide increases cholesterol and triglycerides short-term. It is not clear whether this effect persists long-term however the current evidence does not indicate this.

Patients should be observed regularly for possible occurrence of blood dyscrasias, liver damage or other idiosyncratic reactions.

Concurrent use of chlorothiazides has been reported to decrease hypercalciuria and to dissolve some calculi.

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

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asymptomatic hyperuricaemia can occur and rarely, gout may be precipitated.

Pregnancy and Lactation:

Category C

The teratogenic and embryotoxic potential of frusemide in humans is unknown and it should not be given during pregnancy unless there are compelling medical reasons.

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with the risk. During the latter part of pregnancy products of this type should only be given on sound indications, and then in the lowest effective dose.

The use of frusemide in lactating mothers should be avoided as it passes into the breast milk.

Due to possible hypotension the patient's ability to drive or operate machinery may be impaired especially at the start of therapy.

Adverse Effects

As with other diuretics, water balance and electrolytes may be disturbed during treatment with frusemide, especially in patients receiving high doses for long periods.

Excessive diuresis may increase, especially in elderly patients and children, disturbances such as headaches, dizziness, dry mouth or visual impairment and symptoms of hypovolaemia. In extreme cases hypovolaemia may lead to dehydration, hypotension, circulatory collapse and especially in elderly patients thrombophilia. However, acute haemodynamic reactions are generally not to be expected with individualised dosage.

All saluretics can cause hypokalaemia, predominantly in cases of low potassium diet and chronic diarrhoea. Patients with diseases such as cirrhosis of the liver are prone to developing potassium deficient states. Surveillance and replacement therapy where appropriate are required. Potassium deficiency symptoms include muscle weakness, varying levels of paralysis, vomiting, constipation, gas accumulation in the stomach or intestine, increased polyuria induced thirst, polydipsia, disturbances of impulse formation and conduction. Severe potassium loss may lead to paralytic ileus and unconsciousness which may lead to coma.

Underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (see interactions) or nutritional inadequacies (excessive restriction of salt intake), may lead to sodium or other electrolyte or fluid deficiencies which may produce a fall in orthostatic blood pressure, calf muscle spasm, anorexia, weakness, dizziness, drowsiness, apathy, vomiting and confusion.

Frusemide may lower the serum calcium level which can trigger a state of increased neuromuscular irritability. Tetany has been observed in very rare cases. Calcium salts may be deposited in the renal tissue (nephrocalcinosis) in premature infants.

As a consequence of increased renal magnesium losses hypomagnesaemia and in rare cases, tetany or cardiac arrhythmia have been observed.

Gastrointestinal System:

Reactions with normal doses are uncommon. They include anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation. Jaundice and acute pancreatitis have been reported but their relationship to frusemide has not been established. Frusemide may increase the bile flow and distend a biliary tree which is already obstructed.

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Central Nervous System:

Dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany frusemide induced diuresis. Tinnitus, reversible impairment and rarely, permanent impairment of hearing have been observed with reduced renal function.

Dermatologic:

Allergic reactions, such as dermatitis, including rash, urticaria and rare cases of exfoliative dermatitis, necrotising angitis, bullous eruption, erythemamultiforme and purpura and pruritus may occasionally occur. Photosensitivity reactions have occasionally been reported.

Haematologic:

Following rare adverse reactions have been observed: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leucopenia, thrombocytopaenia, agranulocytosis and interstitial nephritis.

Urinary System:

Excessive diuresis and dehydration could cause transient elevation of creatinine and BUN and reduction of GFR. Acute urinary retention with overflow incontinence may occur in elderly men with prostatic hypertrophy. Interstitial nephritis has also been reported.

Pronounced diuresis may trigger or aggravate symptoms of existing obstructed micturition in patients with conditions such as prostatic hypertrophy, ureterostenosis or hydronephrosis.

Cardiovascular:

Orthostatic hypotension may occur and may be aggravated by alcohol, narcotics and barbiturates. Ischaemic complications have also been reported in elderly patients.

Other:

Restlessness, hyperuricaemia, fever, transient rises in serum cholesterol and triglyceride. Treatment with frusemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest. Pre-existing metabolic alkalosis may be aggravated. Uricaemia may occur and lead to gout attacks in predisposed patients

Anaphylactic shock is rare but acutely life-threatening if it does occur.

Whenever adverse reactions are moderate or severe, the frusemide dosage should be reduced or therapy withdrawn.

Interactions

Concurrent administration of a cardiac glycoside increases the sensitivity of the myocardium to digitalis through potassium or magnesium deficiency. Administration of a glucocorticoid during diuretic treatment has a potassium-lowering effect (see Precautions). Use of laxatives over long periods may also predispose a patient to hypokalaemia.

Patients receiving high doses of salicylates in conjunction with frusemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Interactions between frusemide and neuromuscular blocking agents have been reported. These seem to be dependent on the dose of frusemide and the neuromuscular blocking agent involved. Low doses of frusemide (0.1-10 µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1-5 mg/kg) of frusemide have a tendency to antagonise the skeletal muscle relaxing effect of tubocurarine but may potentiate the action of succinylcholine. Clinical relevance of these findings is uncertain.

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Lithium should not be given with diuretics as they reduces its renal clearance and therefore add a high risk of lithium toxicity.

Especially in the presence of impaired renal function frusemide may increase the ototoxic potential of antibiotics. Avoid this combination (except in life-threatening situations) as the sequelae may be irreversible.

As frusemide may enhance nephrotoxicity of certain antibiotics (e.g. aminoglycosides, cephaloridine), simultaneous administration is not advisable.

Combination of frusemide and amphotericin can result in an excessive loss of potassium.

Frusemide may decrease arterial responsiveness to noradrenaline. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

The action of other antihypertensive may be increased by frusemide, especially in combination with ACE Inhibitors. Administration of ACE Inhibitors to patients pretreated with frusemide may lead to deterioration of renal function.

Non steroidal anti-inflammatory drugs (e.g. indomethacin, acetylsalicylic acid) and probenecid may reduce the natriuretic and antihypertensive effects of frusemide in some patients by inhibiting prostaglandin synthesis. NSAID's may also cause renal failure in case of pre-existing hypovolaemia.

Concomitant use of frusemide with ethacrynic acid or cisplatin should be avoided due to the possibility of ototoxicity. If frusemide is used in combination with cisplatin to force diuresis, care must be taken that only a low dose (e.g. 40mg with normal kidney function) of frusemide is used and that there is a positive fluid balance.

Anticonvulsants like phenytoin may decrease the response to frusemide. A combination of frusemide and chloral hydrate may lead to diaphoresis, sensation of heat, flushes, nausea, tachycardia and increased blood pressure.

Frusemide may attenuate the effect of antidiabetics or pressor amines (e.g. adrenaline nor adrenaline).

Concurrent administration of frusemide and sucralfate should be avoided. Sucralfate reduces the absorption of frusemide and therefore weakens its effect.

It is appropriate to monitor serum theophylline levels as the steady state concentration of theophylline may be raised when the medicines are given together.

Overdosage

The principal signs and symptoms of overdose with frusemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalaemia and hypochloreaemic alkalosis, and extensions of its diuretic action The concentration of frusemide in biological fluids is associated with toxicity or death.

Treatment of overdosage is largely supportive and consists of replacement of excessive fluid and electrolyte loss. Blood pressure, carbon dioxide level and serum electrolytes should be determined frequently. In patients with urinary bladder outlet obstruction (e.g. prostatic hypertrophy) adequate drainage must be assured. Frusemide elimination is not accelerated by haemodialysis.

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Pharmaceutical Precautions

Store below 30°C.
Protect from heat, light and moisture.
Keep container tightly closed.

Medicine Classification

Prescription-Only Medicine

Package Quantities

APO-FRUSEMIDE 40mg tablets
Bottles of 50, 500 and 1000 tablets.

Further Information

Tablets contain Lactose and Wheat Starch.

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