PRODUCT MONOGRAPH

NTP-FUROSEMIDE

(Furosemide)

Tablets, 20, 40 and 80 mg

Diuretic

Teva Canada Limited
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NAME OF DRUG

NTP- FUROSEMIDE

(Furosemide)

Tablets 20, 40 and 80 mg

THERAPEUTIC CLASSIFICATION

Diuretic

ACTIONS

NTP-FUROSEMIDE (furosemide) is a potent diuretic. It inhibits sodium reabsorption at the level of the ascending limb of Henle's loop and at the
-level of the proximal and distal convoluted tubules.

The action on the distal tubule is independent of a carbonic anhydrase or aldosterone inhibitory action.

Following oral administration the diuresis starts within one hour, the maximum effect occurs between one and two hours and lasts 6 to 8 hours.

INDICATIONS

NTP-FUROSEMIDE. (furosemide) is indicated for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, nephrosis and chronic nephritis, as well as other edematous states amenable to diuretic therapy. Furosemide can also be used alone in the control of mild to moderate hypertension and/or in combination with other antihypertensives in more severe cases. Hypertensive patients who cannot be adequately controlled by thiazides will probably also not be adequately controllable with furosemide alone.

CONTRAINDIICATIONS

NTP-FUROSEMIDE (furosemide) is contraindicated in complete renal shutdown. If increasing azotemia and oliguria occur during treatment of progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or

corrected. Furosemide is also contraindicated in patients with a known history of hypersensitivity to furosemide.

As furosemide may be capable of displacing bilirubin from albumin at least "in vitro", it should not be administered to jaundiced newborn infants or to infants suffering from diseases (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) with the potential of causing hyperbilirubinemia and possibly kernicterus.

WARNINGS

NTP-FUROSEMIDE (FUROSEMIDE) IS A POTENT DIURETIC WHICH IF GIVEN IN EXCESS DOSAGE CAN LEAD TO PROFOUND DIURESIS WITH WATER AND ELECTROLYTE DEPLETION. THEREFORE, CAREFUL MEDICAL SUPERVISION IS REQUIRED AND DOSE AND DOSAGE SCHEDULE SHOULD BE ADJUSTED TO THE INDIVIDUAL PATIENT'S REQUIREMENTS (SEE DOSAGE AND ADMINISTRATION) •

The teratogenic and embryotoxic potential of furosemide in humans is unknown. The drug should not be used in pregnant women or in women of childbearing potential unless in the opinion of the attending physician the benefits to the patient outweigh the possible risk to the foetus (see REPRODUCTIVE AND TERATOLOGICAL STUDIES).

It has been reported that furosemide is excreted into breast milk.Alternatives to breast feeding should be considered for mothers receiving furosemide.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effects of tubocurarine. Excerise caution in administering curare or derivatives during furosemide therapy. Discontinue furosemide for 1 week prior to elective surgery.

PRECAUTIONS

Excessive diuresis induced by NTP-FUROSEMIDE (furosemide) may result in dehydration and reduction of blood volume with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. Furosemide may cause electrolyte depletion. Frequent serum electrolyte and C02 determinations should be performed during the first few months of therapy and periodically thereafter) and abnormalities corrected or the drug temporarily withdrawn. Potassium supplements may be required especially when high doses are used over prolonged periods. Particular caution with potassium levels is necessary when the patient is on digitalis glycosides, potassium-depleting steroids, or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be
required.

It may be advisable to hospitalize patients with hepatic cirrhosis and ascites prior to initiating therapy. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Since rigid sodium restriction is conducive to both hyponatremia and hypokalemia such restriction is not advisable in patients on furosemide therapy.

Furosemide may lower serum calcium levels and rare cases of tetany have been reported; periodic serum levels should be obtained.

Periodic checks on urine and blood glucose should be made in diabetics and in those suspected of latent diabetes when receiving furosemide. Increases in blood glucose) and alterations in glucose tolerance tests with abnormalities of the fasting and 2-hour postprandial blood sugar levels have been observed. Rare cases of precipitation of diabetes mellitus have been reported.

Frequent monitoring of BUN levels is advisable since reversible elevations may occur.

During furosemide administration hyperuricemia may occur and in rare cases gout may be precipitated.

In hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dosage of these drugs when furosemide is given as it .potentiates their hypotensive effect.

Recent evidence suggests that furosemide may potentiate the nephrotoxic properties of cephaloridine; concomitant administration of these two agents should therefore be avoided.

Indomethacin may reduce the natriuretic and antihypertensive effects of furosemide.Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and furosemide should be observed closely to determine if the desired diuretic and/or ntihypertensive effect of furosemide is achieved.

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

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

As furosemide is a sulfonamide derivative, it should be used with caution in patients with known hypersensitivity to other antibacterial, diuretic, or hypoglycemic sulfonamide derivatives.

Furosemide in high doses is known to have ototoxic potential. (See ADVERSE REACTIONS SECTION).

ADVERSE REACTIONS

NTP-FUROSEMIDE (furosemide) can cause excessive diuresis and electrolyte depletion (See WARNINGS AND PRECAUTIONS). Electrolyte depletion may manifest itself by weakness, fatigue, thirst, dizziness, lethargy, leg cramps, anorexia, vomiting and mental confusion.

Cases of deafness, tinnitus and vertigo have been reported when furosemide was given parenterally at doses exceeding the usual therapeutic dose.

Deafness is more likely to occur in patients with severe impairment of renal function and in patients who are also receiving drugs known to be ototoxic.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen; these have been observed in association with dehydration which should be avoided, especially in patients with renal insufficiency.

Various forms of dermatitis, including urticaria, rare cases of exfoliative dermatitis and pruritus have been reported.

Paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea may occur. Anemia, leukopenia, aplastic anemia and thrombocytopenia (with purpura) have occurred, as well as rare cases of agranulocytosis which responded to treatment.

Furosemide-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, bladder spasm and symptoms of urinary frequency.

In addition, the following rare adverse effects have been reported (however, relationship to the drug has not been established with certainty): sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, acute pancreatitis, thrombophlebitis and emboli.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Dehydration and electrolyte depletion may be caused by overdosage accidental ingestion.

Treatment: Discontinue drug and institute water and electrolyte replacement.

DOSAGE AND ADMINISTRATION

Edema: Adults: The usual initial oral dose is 40 mg to 80 mg in a single dose preferably in the morning. If diuresis has not occurred, increase dosage by 40 mg increments, if necessary as frequently as every 6 hours.

The effective dose can then be repeated 1 to 3 times daily. Do not exceed a maximum daily dose of 200 mg. This dosage and dosage schedule can be maintained or even reduced according to the patient's response. An intermittent dosage schedule of 2 to 4 consecutive days each week may be utilized. Frequent clinical and laboratory observations are necessary in patients receiving doses exceeding 120 mg/day.

Children: Institute oral furosemide in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes.

The single oral dose should be in the range of 0.5 to 1 mg/kg. The daily oral dose (given in divided doses 6 to 12 hours apart) should not exceed 2 mg/kg. Adopt an intermittent dosage schedule as soon as possible, using the minimum effective dose at the longest possible drug free interval.

Hypertension: The usual adult dose is 40 mg twice daily for initiation of therapy and for maintenance. If 40 mg twice daily does not lead to a clinically satisfactory response, add other antihypertensive agents. Conduct careful observations for blood pressure changes when furosemide is used with other antihypertensive drugs, especially during initial therapy.

When adding furosemide to the treatment of patients under therapy with other antihypertensives, reduce the dosage of the other agents. As the blood pressure falls under the effect of furosemide, a further dosage reduction, or even discontinuation of other antihypertensive drugs may be necessary.

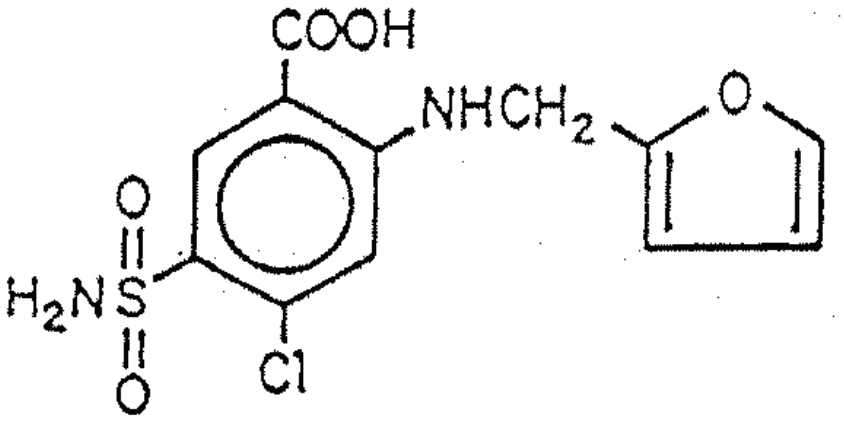
AVAILABILITY

NTP-FUROSEMIDE (furosemide) is supplied as white, round, scored tablets of 20 mg, yellow, round, scored tablets of 40 mg and yellow elongated tablets of 80 mg in bottles of 100 and 1000.

NOTE: Dispense in tight, light-resistant containers.

CHEMISTRY

Furosemide Structure:



Molecular Formula: CIZHIICINZOSS **Molecular** Weight: 330.75.

Chemical Name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

Description: Furosemide is a white or almost white, crystalline powder, odourless and almost tasteless. Practically insoluble in water, sparingly soluble in alcohol, slightly soluble in ether, very slightly soluble in chloroform.

PHARMOCOLOGY

Absorption, Metabolism and Excretion:

Furosemide is readily absorbed from the gastrointestinal tract and bound to plasma proteins. The diuretic response is apparent within one hour after oral ingestion with a peak effect occurring in the first or second hour. Following the oral administration of 40 mg of furosemide, the average peak serum level was 0.989 mcg/mL after one hour. The duration of action of furosemide is 4 to 6 hours, but may continue up to 8 hours.

Approximately 2/3 of the ingested furosemide is excreted in the urine by both glomerular filtration and proximal tubular secretion. One-third of the ingested dose is excreted in the feces. Only a small fraction is metabolized by cleavage of the side chain.

Renal Pharmacology:

Furosemide had no significant pharmcological effects other than on the renal function.

In dogs, furosemide demonstrated diuretic properties. Diuresis and sodium excretion were induced by doses of 0.125 mg/kg administered intravenously or 0.5 mg/kg administered orally.

Maximum water and sodium excretion is obtained by oral and intravenous doses of 12.5 and 25 mg/kg respectively. Increased potassium excretion can only be demonstrated with doses exceeding 1 rng/kg. The onset of action is rapid after intravenous and oral administration and the duration of activity is approximately 2 and 4 hours respectively.

Furosemide produces an immediate diuresis after intravenous administration and is effective unilaterally after injection into a renal artery. Its action, therefore, is directly on the kidney. The diuretic response is prompt and relatively brief. At the peak of diuretic response 30 to 40% of the filtered sodium load may be excreted, along with some potassium and with chloride as the major anion. Furosemide augments the potassium output as a result of increased distal potassium secretion. Its diuretic action is independent of changes in acid-base balance. Under conditions of acidosis or alkalosis the diuretic produces a chloruresis without augmentation of bicarbonate excretion.
It does not inhibit carbonic anhydrase.
On the basis of changes in free-water production furosemide inhibits sodium reabsorption in the ascending loop of Henle. However, proximal sites of action may also be involved, as determined by micropuncture. Partial distal inhibition of sodium reabsorption is also possible. It also decreases the urinary excretion of uric acid and prolonged administration may lead to hyperuricemia. Since urate is transported in the proximal tubule the effect of the drug on uric acid excretion further suggests a proximal tubule site of action.

Administration of furosemide may induce extracellular metabolic alkalosis, primarily by virtue of the disproportionate loss of chloride but also, in part, as a result of the variable depletion of potassium.

TOXICOLOGY

Acute Toxicity:

LD_{50}(oral route)	Species	Dose
	Mice	2.108 g/kg
	Rats	2.20 g/kg

Signs of acute intoxication in the mouse and rat included marked increase in muscle tone, marked eye ptosis, severe muscle spasms, moderate CNS depression and acute clonic convulsions.

Furosemide has been reported to be more toxic in newborn than adult rats.

Chronic Toxicity - rats:
Five groups of twenty weanling Wistar rats (10 males and 10 females) received 0, 50, 100, 200 and 400 mg/kg daily, five days a week for a year.Furosemide was administered by intragastric tube in an aqueous suspension.

During the first week a majority of the rats on the highest dose and 50% of the group receiving 200 mg/kg showed toxic manifestations; ocular discharge, lethargy, anorexia, dyspnea and weight loss.

Drug related mortality was 5, 10 and 50% in the 100, 200 and 400 mg/kg group respectively. The majority of the highest dose animals died within 10 days of initiating therapy. Histological examination of those animals dying early revealed renal and cardiac lesions, possibly due to electrolyte depletion.

A significant and dose related increase in the relative weight of the kidneys was seen. Drug-induced lesions were seen in the heart and kidney. Histological examination of the kidneys showed degenerative changes of the tubular epithelium, characterized by swollen epithelial cells with increased cytoplasmic density. Occasionally focal necrosis of the epithelium and decreased cell size were evident, plus accumulation of some calcified material. This lesion was frequently found in the two highest dose groups and only rarely in the other groups. The myocardium showed areas of severe focal fibrosis similar to those found in potassium deficiency.

Chronic toxicity: - dogs:
Five groups of four beagle dogs received respectively 0, 10, 30, 100 and 350 mg/kg of furosemide in capsules five days per week for six months.

Blood urea nitrogen and blood sugar levels were elevated in animals on the highest dose. Values returned to normal after treatment was terminated.

The most consistent pathological findings were renal lesions consisting of calcification and scarring of the renal parenchyma at all doses above 10 mg/kg.

Reproductive and Teratology Studies

The effect on furosemide on embryonic and fetal development and on pregnant dams was studied in mice, rats, and rabbits.

Furosemide caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and in some cases of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control groups. (See WARNINGS).

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