PRODUCT MONOGRAPH

[Pr]pms-FUROSEMIDE

(Furosemide Tablets)

20 and 40 mg

Diuretic

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THERAPEUTIC CLASSIFICATION

Diuretic

ACTION AND CLINICAL PHARMACOLOGY

Furosemide is a potent diuretic. Pharmacological experiments have shown that it acts not only at the proximal and distal tubules but also at the ascending limb of Henle's loop. It has been demonstrated that Furosemide inhibits primarily the re-absorption of sodium. The action of the distal tubules is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

Following oral administration, the peak effects occurs within 1-2 hours, and the duration of diuretic effect is 6-8 hours.

INDICATIONS AND CLINICAL PHARMACOLOGY

pms-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 which are amenable to diuretic therapy. pms-FUROSEMIDE can also be used alone in the control of mild to moderate hypertension and/or in combination with other antihypertensive agents in more severe cases. Hypertensive patients which cannot be adequately controlled by thiazides will probably also not be adequately controllable with furosemide alone.

CONTRAINDICATIONS

pms-FUROSEMIDE (furosemide) is contraindicated in patients with complete renal shutdown. If increasing azotemia and oliguria occur during treatment of progressive renal disease, pms-FUROSEMIDE should be discontinued. Therapy with pms-FUROSEMIDE should not be initiated in patients with hepatic coma or in states of electrolyte depletion until the basic condition is improved or corrected. pms-FUROSEMIDE is also contraindicated in patients with a known history of hypersensitivity to this compound.

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 disease (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) With the potential of causing hyperbilirubinemia and possibly kernioterus.

WARNINGS

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.

Teratogenic and embryotoxic potential of furosemide in humans is unknown. This 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 fetus. (See **Reproductive and Teratological Studies in Animals**).

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effects of tubocurarine. Exercise caution in administering curare or derivatives during furosemide therapy. It is advisable to discontinue furosemide for one week prior to elective surgery.

PRECAUTIONS

Excessive diuresis induced by 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 CO_2 should be determined during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

During long-term therapy a high potassium diet is recommended. Potassium supplements may be required especially when high doses are used for 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 calcium levels should be obtained.

Cases of tinnitus and reversible deafness have been report. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness was usually insidious and gradually progressive up to 6 months after furosemide therapy. Hearing impairment is more likely to occur

in patients with severely reduced renal function who are given large doses of furosemide parenterally or in patients who are also receiving drugs know to be ototoxic.

Periodic checks on urine and blood glucose should be made in diabetics and even in suspected latent diabetics receiving furosmide. 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 BUN determinations during the first few months of therapy and periodically thereafter are advisable.

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

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.

Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competition for renal excretory sites.
As fusosemide is a sulfonamide derivative, it should be used with caution in patients with known hypersensitivity to other antibacterial, diuretic or hypoglycemic sulfonamide derivatives.

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

ADVERSE EFFECTS

Furosemide can cause excessive diuresis and/or electrolyte depletion (See **Warnings and Precautions**). Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting and/or mental confusion.

Cases of reversible deafness, tinnitus and vertigo have been reported. Deafness is more likely to occur in patients with severe impairment of renal function and in patients who are receiving drugs known to be ototoxic (see **Precautions**).

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

Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis and pruritus did occur. Paresthesis, blurring of vision, postural hypotension, nausea, vomiting or diarrhea may occur. Anemia, leukopenia, aplastic anemia and thrombocytopenia (with purpura) have been reported, 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 report (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 & TREATMENT OF OVERDOSAGE

Dehydration and electrolyte depletion may be caused by overdosage or accidental ingestion. Discontinue the drug. Institute water and electrolyte replacement.

DOSAGE AND ADMINISTRATION

Edema: Adults

The usual initial oral dose (adult) of pms-FUROSEMIDE (furosemide) is 40-80mg given in a single dose preferably in the morning. If diuresis has not occurred, increase dosage by increments of 40mg, if necessary as frequently as every 6 hours. The effective dose can then be repeated one to three times daily. A maximum daily dose of 200mg should not be exceeded. This dosage and dosage schedule can be maintained or even reduced according to the patient's response. An intermittent dosage schedule of 2-4 consecutive days each week may be utilized. Frequent clinical and laboratory observations are necessary in patients receiving doses exceeding 120mg per day.

Children:

Oral pms-FUROSEMIDE should be instituted 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 1mg/kg. The daily oral dose (given in divided doses 6 to 12 hours apart) should not exceed 2mg/kg/day. An intermittent dosage schedule should be adopted as soon as possible, using the minimum effective dose at the longest possible drug free interval.

Hypertension:

The usual adult dose of pms-FUROSEMIDE is one tablets (40mg) twice daily both for initiation of therapy and for maintenance. If one tablet (40mg) twice daily does not lead to a clinically satisfactory response, other antihypertensive agents should be added. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

When adding pms-FUROSEMIDE to the treatment of patients under therapy with other antihypertensives, the dosage of the other agents must be reduced. As the blood pressure falls

under the added effect of pms-FUROSEMIDE, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

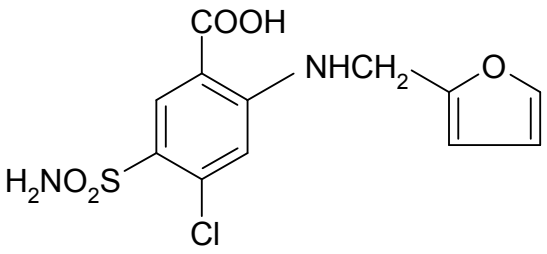
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Furosemide

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

Structural Formula:



Molecular Formula: $C_{12}H_{11}ClN_20_5S$ Molecular Weight: 330.75

Description: A.white or almost white, crystalline powder, odourless, and almost tasteless.

Solubility: Soluble in alcohol and ether, practically insoluble in water and chloroform.

Stability and Storage Recommendations:

Store pms-FUROSEMIDE (furosemide) Tablets at controlled room temperature (15°to 30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

20mg tablets: each white, compressed tablet, imprinted "p" over 20 contains 20mg of furosemide. Available in size of 500 tablets.

40mg tablets: each yellow, scored, compressed tablets, imprinted "p" over 40 contains 40mg of furosemide. Available in size of 500 tablets.

PHARMACOLOGY

Absorption, Metabolism & Excretion:

Furosemide is rapidly absorbed from the gastro-intestinal tract. The diuretic effect of furosemide is apparent within one hour following oral administration and the peak effect occurs in the first or second hour. The duration of action is 4-6 hours but may continue up to 8 hours. Following intravenous administration of the drug, the diuresis occurs within 30 minutes and the duration of action is about 2 hours.

Although urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion together this accounts for roughly only 2/3 or the ingested dose, the remainder is excreted in the feces. A small fraction is metabolised by cleavage of the side chain.

RENAL PHARMACOLOGY:

Furosemide has no significant pharmacological effects other then on the renal function.

In dogs, furosemide demonstrated diuretic properties. Diuresis and sodium excretion were induced by doses of 0.125mg/kg administeted intravenously or 0.5mg/kg administered orally. Maximum water and sodium excretion is obtained by oral and intravenous doses of 12.5 and 25mg/kg respectively. Increased potassium excretion can only be demonstrated with doses exceeding 1mg/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 30-40% 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 independant of changes in acid-base balance. Under conditions of acidosis or alkalosis the diruretic 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 hyperucicemia. 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 Toxicology:

The oral LD_{50} of furosemide in mice was found to be 1740mg/kg. Ten rats received doses up to 6000mg/kg by oral route: one animal died at 3200mg/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.

The LD_{50} of furosemide is lower in newborn than in adult rats.

Subacute Toxicity - Rats:

Three groups of 12 rats each (males and females in equal numbers) received oral doses of 0, 50 or 20mg/kg for 30 days. A noticeable suppression in body weights and exhaustion, possibly due to excessive diuresis, was observed particularly at eh 200mg/kg dose. Histopathological examination showed incidence of chronic prostatitis, 4 rats; chronic pericarditis, 4 rats; hydronephrosis, 2 rats; and focal liver cecrosis, 1 rat. In the control group, a singular incidence of chronic prostatis, focal liver necrosis and hydronephrosis was observed.

Chronic Toxicity - Rats

Five groups of 20 weanling wistar rats (10 males and 10 females) received daily doses of 0, 50, 100, 200 and 400mg/kg of furosemide, 5 days per week, for 52 weeks. The drug was administered in an aqueous suspension by intragastric intubation.

During the first week of administration of the drug, most of the rats in the 400mg/kg dose group and approximately half of the rats in the 200mg/kg group exhibited signs of illness such as ocular discharge, lethargy, anorexia, dyspnea and loss of weight. Drug induced deaths were one, two and ten of twenty animals which died during treatment demonstrated kidney and heart lesions possibly due to electrolyte depletion. There was a significant reduction in the growth rate in the two highest dose groups. Food intake after an initial reduction returned to normal in these

animals. Slight to moderate increases in hemoglobin, hematocrit, erythrocyte and leucocyte counts were observed in 400mg/kg and 200mg/kg groups.

A significant and dose related increase in the relative weight of the kidneys was seen. Drug-indicated lesions were seen in the heart and kidney. Histopathologically the myocardium showed areas of severe focal fibrosis similar to those found in potassium deficiency. The kidneys showed degenerative changes of the tubular epithelium characterized by swollen epithelial cells, with increased cytoplasmic density. This lesion was frequently found in the two highest dose groups and only rarely in the other groups.

Chronic Toxicity - Dogs:

Five groups of four beagle dogs received capsules of 0, 10, 30, 100 and 350mg/kg.

During the first week of medication, the animals on the highest dose level (350mg/kg) of drug, developed anorexia, general weakness and partial paralysis of the hind legs. This was accompanied by decreased serum sodium and potassium levels and loss of body weight. The dose was reduced to 250mg/kg after two of four dogs died.

Initially a dose related decrease in body weight and reduced food intake occurred which returned to normal after four weeks.

Blood urea nitrogen and blood sugar levels were elevated in animals on the highest dose. Values returned to normal after treatment was terminated. The urinalysis values remained normal throughout the experiment except for urine volume, creatinine and electrolytes changes were consistent with the action of a diuretic-saluretic drug.

Pathological examination of the entire group showed no marked or consistent effect on organ weights. The renal lesions consistent with the chronic administration of the drug and its continuous diuretic action.

Reproductive and Teratological Studies in Animals

Rabbits: The studies in rabbits suggested that fetal lethality mig precede maternal death. Unexplained maternal deaths and abortions resulted from doses of 25 or 50mg/kg in two investigations. At the higher dose of 100mg/kg none of the pregnant animals survived.

Increases incidence of hydronephrosis (distention of renal pelvis and in some cases of the ureters) in fetuses derived from furosemide treated dams was observed when compared to the fetuses derived from the control rabbits.

Mice: Increased incidence of hydronephrosis was also observed.

Other Species: Furosemide had no teratogenic effect in dogs and rats.