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65 EDITION

2011

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NOVARTIS EXHIBIT 1580
Novartis v. Regents, IPR2023-01347
Page 1 of 5

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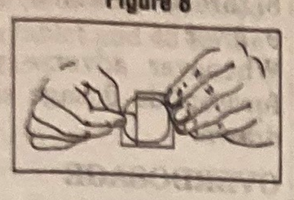
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4. **Peel:** Peel off both parts of the protective liner from the patch. Each fentanyl transdermal system has a clear plastic liner that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this liner off. Throw the clear plastic liner away. **Touch the sticky side of a fentanyl transdermal system as little as possible** (see Figure 8).

Figure 8



5. **Press:** Press the patch onto the chosen skin site **with the palm of your hand and hold there for at least 30 seconds** (see Figure 9). Make sure it sticks well, especially at the edges.

Figure 9



- Fentanyl transdermal system may not stick to all patients. You need to check the patches often to make sure that they are sticking well to the skin.
- If the patch falls off right away after applying, throw it away and put a new one on at a different skin site (see Disposing a Fentanyl Transdermal System).
- If you have a problem with the patch not sticking
  - Apply first aid tape only to the edges of the patch.
  - If you continue to have problems with the patch sticking, you may cover the patch with Bioclusive® or Askina®Derm. These are special see-through adhesive dressings. **Never cover a fentanyl transdermal system with any other bandage or tape.** Remove the backing from the Bioclusive® or Askina®Derm dressing and place it carefully over the fentanyl transdermal system, smoothing it over the patch and your skin.
- **If your patch falls off later, but before 3 days (72 hours) of use, discard it properly (see Disposing a Fentanyl Transdermal System) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).**

6. Wash your hands when you have finished applying a fentanyl transdermal system.

7. Remove a fentanyl transdermal system after wearing it for 3 days (72 hours) (see "Disposing a Fentanyl Transdermal System"). Choose a **different** place on the skin to apply a new fentanyl transdermal system and repeat Steps 2 through 6.

Do not apply the new patch to the same place as the last one.

Water and Fentanyl Transdermal System

- You can bathe, swim or shower while you are wearing a fentanyl transdermal system. If the patch falls off before 3 days (72 hours) after application, discard it properly (see Disposing a Fentanyl Transdermal System) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).

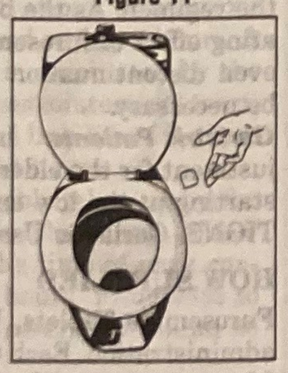
Disposing a Fentanyl Transdermal System

- Fold the used fentanyl transdermal system in half so that the sticky side sticks to itself (Figure 10). **Flush the used fentanyl transdermal system down the toilet right away** (Figure 11).

Figure 10



Figure 11



A used fentanyl transdermal system CAN be VERY dangerous for or even lead to death in babies, children, pets, and adults who have not been prescribed fentanyl transdermal system.

- Throw away any fentanyl transdermal systems that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch and remove the protective liner. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet.** Do not flush the pouch or the protective liner down the toilet. These items can be thrown away in a trash can.

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Askina®Derm is a registered trademark of BBraun Melsungen AG
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED DECEMBER 2009
MG:FTS:R3

FUROSEMIDE TABLETS, USP

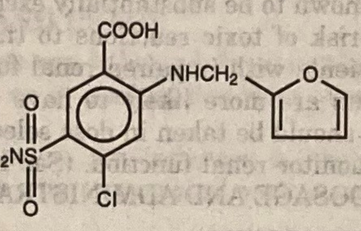
20 mg, 40 mg and 80 mg
℞ only

WARNING

Furosemide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule must be adjusted to the individual patient's needs. (See DOSAGE AND ADMINISTRATION.)

DESCRIPTION

Furosemide is a diuretic which is an anthranilic acid derivative. Chemically, it is 4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid. Furosemide, USP is a white to slightly yellow odorless, crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids. The structural formula is as follows:



$C_{12}H_{11}ClN_2O_5S$
M.W. 330.75

Each tablet for oral administration contains 20 mg, 40 mg or 80 mg of furosemide, USP and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, pregelatinized starch and stearic acid.

Furosemide Tablets, USP 20 mg, 40 mg and 80 mg meet *USP DISSOLUTION TEST 1.*

CLINICAL PHARMACOLOGY

Investigations into the mode of action of furosemide have utilized micropuncture studies in rats, stop flow experiments in dogs and various clearance studies in both humans and experimental animals. It has been demonstrated that furosemide inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle. The high degree of efficacy is largely due to the unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

Recent evidence suggests that furosemide glucuronide is the only or at least the major biotransformation product of furosemide in man. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 mcg/mL are 91% to 99% bound in healthy individuals. The unbound fraction averages 2.3% to 4.1% at therapeutic concentrations.

The onset of diuresis following oral administration is within one hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

In fasted normal men, the mean bioavailability of furosemide from furosemide tablets and furosemide oral solution is 64% to 60%, respectively, of that from an intravenous injection of the drug. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses. The terminal half-life of furosemide is approximately 2 hours.

Significantly more furosemide is excreted in urine following the IV injection than after the tablet or oral solution. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

Geriatric Population: Furosemide binding to albumin may be reduced in elderly patients. Furosemide is predominantly excreted unchanged in the urine. The renal clearance of furosemide after intravenous administration in older healthy male subjects (60 to 70 years of age) is statistically significantly smaller than in younger healthy male subjects (20 to 35 years of age). The initial diuretic effect of furosemide in older subjects is decreased relative to younger subjects. (See PRECAUTIONS: Geriatric Use.)

INDICATIONS AND USAGE

Edema: Furosemide is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Furosemide is particularly useful when an agent with greater diuretic potential is desired.

Hypertension: Oral furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with furosemide alone.

CONTRAINDICATIONS

Furosemide is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide.

WARNINGS

In patients with hepatic cirrhosis and ascites, furosemide therapy is best initiated in the hospital. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alteration 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.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, furosemide should be discontinued.

Cases of tinnitus and reversible or irreversible hearing impairment have been reported. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults, an infusion rate not exceeding 4 mg furosemide per minute has been used).

PRECAUTIONS

General: Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. As with any effective diuretic, electrolyte depletion may occur during furosemide therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with furosemide, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated.

Patients allergic to sulfonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver or kidney damage or other idiosyncratic reactions.

Information for Patients: Patients receiving furosemide should be advised that they may experience symptoms from excessive fluid and/or electrolyte losses. The postural hypotension that sometimes occurs can usually be managed by getting up slowly. Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia. Patients with diabetes mellitus should be told that furosemide may increase blood glucose levels and thereby affect urine glucose tests. The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide.

Hypertensive patients should avoid medications that may increase blood pressure, including over-the-counter products for appetite suppression and cold symptoms.

Laboratory Tests: Serum electrolytes, (particularly potassium), CO_2, creatinine and BUN should be determined frequently during the first few months of furosemide therapy and periodically thereafter. Serum and urine electrolyte determinations are particularly important when the patient is

NOVARTIS EXHIBIT 1580
Novartis v. Regents, IPR2023-01347
Page 3 of 5

For the latest PDR product information, visit PDR.net

vomiting profusely or receiving parenteral fluids. Abnormalities should be corrected or the drug temporarily withdrawn. Other medications may also influence serum electrolytes.

Reversible elevations of BUN may occur and are associated with dehydration which should be avoided, particularly in patients with renal insufficiency.

Urine and blood glucose should be checked periodically in diabetics receiving furosemide, even in those suspected of latent diabetes.

Furosemide may lower serum levels of calcium (rarely cases of tetany have been reported) and magnesium. Accordingly, serum levels of these electrolytes should be determined periodically.

Drug Interactions: Furosemide may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function. Except in life threatening situations, avoid this combination.

Furosemide should not be used concomitantly with ethacrynic acid because of the possibility of ototoxicity. Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.

Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

Furosemide may add to or potentiate the therapeutic effect of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Furosemide may decrease arterial responsiveness to norepinephrine. However, norepinephrine may still be used effectively.

Simultaneous administration of sucralfate and furosemide tablets may reduce the natriuretic and antihypertensive effects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate should be separated by at least 2 hours.

One study in six subjects demonstrated that the combination of furosemide and acetylsalicylic acid temporarily reduced creatinine clearance in patients with chronic renal insufficiency. There are case reports of patients who developed increased BUN, serum creatinine and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIDs.

Literature reports indicate that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of furosemide in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and furosemide should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. A small but significantly increased incidence of mammary gland carcinomas occurred in female mice at a dose 17.5 times the maximum human dose of 600 mg. There were marginal increases in uncommon tumors in male rats at a dose of 15 mg/kg (slightly greater than the maximum human dose) but not at 30 mg/kg.

Furosemide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce sister chromatid exchange in human cells *in vitro*, but other studies on chromosomal aberrations in human cells *in vitro* gave conflicting results. In Chinese hamster cells it induced chromosomal damage but was questionably positive for sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive. The urine of rats treated with this drug did not induce gene conversion in *Saccharomyces cerevisiae*.

Furosemide produced no impairment of fertility in male or female rats at 100 mg/kg/day (the maximum effective diuretic dose in the rat and 8 times the maximal human dose of 600 mg/day).

Pregnancy: ***Teratogenic Effects. Pregnancy Category C:*** Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the maximal recommended human dose. There are no adequate and well controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of furosemide on embryonic and fetal development and on pregnant dams were studied in mice, rats and rabbits.

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (two times the maximal recommended human dose of 600 mg/day). In another study, a dose of 50 mg/kg (four times the maximal recommended human dose of 600 mg/day) also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality that can precede maternal deaths.

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

Nursing Mothers: Because it appears in breast milk, caution should be exercised when furosemide is administered to a nursing mother.

Geriatric Use: Controlled clinical studies of furosemide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. (See PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Adverse reactions are categorized below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions

1. hepatic encephalopathy in patients with hepatocellular insufficiency
2. pancreatitis
3. jaundice (intrahepatic cholestatic jaundice)
4. anorexia
5. oral and gastric irritation
6. cramping
7. diarrhea
8. constipation
9. nausea
10. vomiting

Systemic Hypersensitivity Reactions

1. systemic vasculitis
2. interstitial nephritis
3. necrotizing angiitis

Central Nervous System Reactions

1. tinnitus and hearing loss
2. paresthesias
3. vertigo
4. dizziness
5. headache
6. blurred vision
7. xanthopsia

Hematologic Reactions

1. aplastic anemia (rare)
2. thrombocytopenia
3. agranulocytosis (rare)
4. hemolytic anemia
5. leukopenia
6. anemia

Dermatologic-Hypersensitivity Reactions

1. exfoliative dermatitis
2. bullous pemphigoid
3. erythema multiforme
4. purpura
5. photosensitivity
6. urticaria
7. rash
8. pruritus

Cardiovascular Reaction

Orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.

Other Reactions

1. hyperglycemia
2. glycosuria
3. hyperuricemia
4. muscle spasm
5. weakness
6. restlessness
7. urinary bladder spasm
8. thrombophlebitis
9. fever

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

OVERDOSAGE

The principal signs and symptoms of overdosage with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of its diuretic action.

The acute toxicity of furosemide has been determined in mice, rats and dogs. In all three, the oral LD_{50} exceeded 1000 mg/kg body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats.

The concentration of furosemide in biological fluids associated with toxicity or death is not known.

Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy).

Hemodialysis does not accelerate furosemide elimination.

DOSAGE AND ADMINISTRATION

Edema: Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response.

Adults: The usual initial dose of furosemide is 20 mg to 80 mg given as a single dose. Ordinarily a prompt diuresis ensues. If needed, the same dose can be administered 6 to 8 hours later or the dose may be increased. The dose may be raised by 20 mg or 40 mg and given not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. The individually determined single dose should then be given once or twice daily (e.g., at 8 am and 2 pm). The dose of furosemide may be carefully titrated up to 600 mg/day in patients with clinically severe edematous states.

Edema may be most efficiently and safely mobilized by giving furosemide on 2 to 4 consecutive days each week.

When doses exceeding 80 mg/day are given for prolonged periods, careful clinical observation and laboratory monitoring are particularly advisable. (See PRECAUTIONS: Laboratory Tests.)

Geriatric Patients: In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range (see PRECAUTIONS: Geriatric Use).

Pediatric Patients: The usual initial dose of oral furosemide in pediatric patients is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended. For maintenance therapy in pediatric patients, the dose should be adjusted to the minimum effective level.

Hypertension: Therapy should be individualized according to the patient's response to gain maximal therapeutic response and to determine the minimal dose needed to maintain the therapeutic response.

Adults: The usual initial dose of furosemide for hypertension is 80 mg, usually divided into 40 mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, add other antihypertensive agents.

Changes in blood pressure must be carefully monitored when furosemide is used with other antihypertensive drugs, especially during initial therapy. To prevent excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50 percent when furosemide is added to the regimen. As the blood pressure falls under the potentiating effect of furosemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Geriatric Patients: In general, dose selection and dose adjustment for the elderly patient should be cautious, usually starting at the low end of the dosing range (see PRECAUTIONS: Geriatric Use).

HOW SUPPLIED

Furosemide Tablets, USP are available as tablets for oral administration. Each tablet for oral administration contains 20 mg, 40 mg or 80 mg of furosemide, USP.

The 20 mg tablets are white, round, unscored tablets debossed with **M2**. They are available as follows:

NDC 0378-0208-93
bottles of 30 tablets
NDC 0378-0208-01
bottles of 100 tablets
NDC 0378-0208-10
bottles of 1000 tablets

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NOVARTIS EXHIBIT 1580
Novartis v. Regents, IPR2023-01347
Page 4 of 5

The 40 mg tablets are white, round, scored tablets debossed with **MYLAN** over **216** on one side of the tablet and **40** on the other side. They are available as follows:
NDC 0378-0216-93
bottles of 30 tablets
NDC 0378-0216-01
bottles of 100 tablets
NDC 0378-0216-10
bottles of 1000 tablets
The 80 mg tablets are white, round, scored tablets debossed with **MYLAN** over **232** on one side of the tablet and **80** on the other side. They are available as follows:
NDC 0378-0232-93
bottles of 30 tablets
NDC 0378-0232-01
bottles of 100 tablets
NDC 0378-0232-05
bottles of 500 tablets
Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]
Protect from light.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Exposure to light may cause slight discoloration. Discolored tablets should not be dispensed.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED JULY 2008
FUR:R26

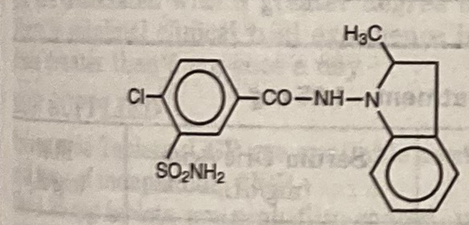
INDAPAMIDE TABLETS, USP

℞

1.25 mg and 2.5 mg
℞ only

DESCRIPTION

Indapamide is an oral antihypertensive/diuretic. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a lipid-soluble methylindoline moiety. It differs chemically from the thiazides in that it does not possess the thiazide ring system and contains only one sulfonamide group. The chemical name of indapamide is 4-Chloro-N-(2-methyl-1-indolinyl)-3-Sulfamoylbenzamide, and its molecular weight is 365.84. The compound is a weak acid, pK_a=8.8, and is soluble in aqueous solutions of strong bases. It is a white to yellow-white crystalline (tetragonal) powder.



$C_{16}H_{16}ClN_3O_3S$

Each tablet, for oral administration, contains 1.25 mg or 2.5 mg of indapamide, USP and the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide. Additionally, the 1.25 mg product contains glyceryl triacetate and D&C Red No. 30 Aluminum Lake and the 2.5 mg product contains triacetin.

CLINICAL PHARMACOLOGY

Indapamide is the first of a new class of antihypertensive/diuretics, the indolines. The oral administration of 2.5 mg (two 1.25 mg tablets) of indapamide to male subjects produced peak concentrations of approximately 115 ng/mL of the drug in the blood within 2 hours. The oral administration of 5 mg (two 2.5 mg tablets) of indapamide to healthy male subjects produced peak concentrations of approximately 260 ng/mL of the drug in the blood within 2 hours. A minimum of 70% of a single oral dose is eliminated by the kidneys and an additional 23% by the gastrointestinal tract, probably including the biliary route. The half-life of indapamide in whole blood is approximately 14 hours.
Indapamide is preferentially and reversibly taken up by the erythrocytes in the peripheral blood. The whole blood/plasma ratio is approximately 6:1 at the time of peak concentration and decreases to 3.5:1 at 8 hours. From 71% to 79% of the indapamide in plasma is reversibly bound to plasma proteins.
Indapamide is an extensively metabolized drug, with only about 7% of the total dose administered, recovered in the urine as unchanged drug during the first 48 hours after administration. The urinary elimination of ^{14}C-labeled indapamide and metabolites is biphasic with a terminal half-life of excretion of total radioactivity of 26 hours.
In a parallel design double-blind, placebo controlled trial in hypertension, daily doses of indapamide between 1.25 mg and 10 mg produced dose related antihypertensive effects. Doses of 5 mg and 10 mg were not distinguishable from each other although each was differentiated from placebo and 1.25 mg indapamide. At daily doses of 1.25 mg, 5 mg and 10 mg, a mean decrease of serum potassium of 0.28, 0.61 and 0.76 mEq/L, respectively, was observed and uric acid increased by about 0.69 mg/100 mL.
In other parallel design, dose-ranging clinical trials in hypertension and edema, daily doses of indapamide between 0.5 mg and 5 mg produced dose related effects. Generally, doses of 2.5 mg and 5 mg were not distinguishable from each other although each was differentiated from placebo and from 0.5 mg or 1 mg indapamide. At daily doses of 2.5 mg and 5 mg a mean decrease of serum potassium of 0.5 and 0.6 mEq/Liter, respectively, was observed and uric acid increased by about 1 mg/100 mL.
At these doses, the effects of indapamide on blood pressure and edema are approximately equal to those obtained with conventional doses of other antihypertensive/diuretics.
In hypertensive patients, daily doses of 1.25 mg, 2.5 mg and 5 mg of indapamide have no appreciable cardiac inotropic or chronotropic effect. The drug decreases peripheral resistance, with little or no effect on cardiac output, rate or rhythm. Chronic administration of indapamide to hypertensive patients has little or no effect on glomerular filtration rate or renal plasma flow.
Indapamide had an antihypertensive effect in patients with varying degrees of renal impairment, although in general, diuretic effects declined as renal function decreased.
In a small number of controlled studies, indapamide taken with other antihypertensive drugs such as hydralazine, propranolol, guanethidine and methyldopa, appeared to have the additive effect typical of thiazide-type diuretics.

INDICATIONS AND USAGE

Indapamide tablets are indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs.
Indapamide tablets are also indicated for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard (see PRECAUTIONS below).
Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.
Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Indapamide is indicated in pregnancy when edema is due to pathologic causes, just as it is in the absence of pregnancy (however, see PRECAUTIONS below). Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is not harmful to either the fetus or the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Anuria. Known hypersensitivity to indapamide or to other sulfonamide-derived drugs.

WARNINGS

Severe cases of hyponatremia, accompanied by hypokalemia have been reported with recommended doses of indapamide. This occurred primarily in elderly females. (See PRECAUTIONS: Geriatric Use.) This appears to be dose related. Also, a large case-controlled pharmacoepidemiology study indicates that there is an increased risk of hyponatremia with indapamide 2.5 mg and 5 mg doses. Hyponatremia considered possibly clinically significant (< 125 mEq/L) has not been observed in clinical trials with the 1.25 mg dosage (see PRECAUTIONS). Thus, patients should be started at the 1.25 mg dose and maintained at the lowest possible dose. (See DOSAGE AND ADMINISTRATION.)
Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS: Hypokalemia), and electrolyte monitoring is essential, particularly in patients who would be at increased risk from hypokalemia, such as those with cardiac arrhythmias or who are receiving concomitant cardiac glycosides.
In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such concomitant therapy.

PRECAUTIONS

General: ***Hypokalemia, Hyponatremia, and Other Fluid and Electrolyte Imbalances:*** Periodic determinations of serum electrolytes should be performed at appropriate intervals. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. Warning signs include dry mouth, thirst, weakness, fatigue, lethargy, drowsiness, restlessness, muscle pains or cramps, hypotension, oliguria, tachycardia, and gastrointestinal disturbance. Electrolyte determinations are particularly important in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance (including those with heart failure, kidney disease, and cirrhosis), and in patients on a salt-restricted diet.
The risk of hypokalemia secondary to diuresis and natriuresis is increased when larger doses are used, when the diuresis is brisk, when severe cirrhosis is present and during concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; the appropriate treatment is restriction of water rather than administration of salt, except in rare instances when the hyponatremia is life threatening. However, in actual salt depletion, appropriate replacement is the treatment of choice. Any chloride deficit that may occur during treatment is generally mild and usually does not require specific treatment except in extraordinary circumstances as in liver or renal disease. Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.
Hyperuricemia and Gout: Serum concentrations of uric acid increased by an average of 0.69 mg/100 mL in patients treated with indapamide 1.25 mg, and by an average of 1 mg/100 mL in patients treated with indapamide 2.5 mg and 5 mg, and frank gout may be precipitated in certain patients receiving indapamide (see ADVERSE REACTIONS below). Serum concentrations of uric acid should, therefore, be monitored periodically during treatment.
Renal Impairment: Indapamide, like the thiazides, should be used with caution in patients with severe renal disease, as reduced plasma volume may exacerbate or precipitate azotemia. If progressive renal impairment is observed in a patient receiving indapamide, withholding or discontinuing diuretic therapy should be considered. Renal function tests should be performed periodically during treatment with indapamide.
Impaired Hepatic Function: Indapamide, like the thiazides, should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Glucose Tolerance: Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium Excretion: Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After 6 to 8 weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Prolonged treatment with drugs pharmacologically related to indapamide may in rare instances be associated with hypercalcemia and hypophosphatemia secondary to physiologic changes in the parathyroid gland; however, the common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulcer, have not been seen. Treatment should be discontinued before tests for parathyroid function are performed. Like the thiazides, indapamide may decrease serum PBI levels without signs of thyroid disturbance.
Interaction with Systemic Lupus Erythematosus: Thiazides have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with indapamide as well.
Drug Interactions:
Other Antihypertensives: Indapamide may add to or potentiate the action of other antihypertensive drugs. In limited controlled trials that compared the effect of indapamide combined with other antihypertensive drugs with the effect of the other drugs administered alone, there was no notable change in the nature or frequency of adverse reactions associated with the combined therapy.
Lithium: See WARNINGS.
Post-Sympathectomy Patient: The antihypertensive effect of the drug may be enhanced in the post-sympathectomized patient.

NOVARTIS EXHIBIT 1580
Novartis v. Regents, IPR2023-01347
Page 5 of 5