PRODUCT MONOGRAPH

NU–INDAPAMIDE

Indapamide Tablets USP

1.25 and 2.5 mg

Diuretic/Antihypertensive Agent

NU-PHARM INC.
50 Mural St., Units 1 & 2
Richmond Hill, Ontario
L4B 1E4

DATE OF PREPARATION:
June 29, 1996
DATE OF REVISION:
November 3, 2009

Control#: 133877

PRODUCT MONOGRAPH

NU–INDAPAMIDE

Indapamide Tablets USP

1.25 and 2.5 mg

THERAPEUTIC CLASSIFICATION

Diuretic/Antihypertensive Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Indapamide is a diuretic antihypertensive agent. The mechanism whereby indapamide exerts its action in the control of hypertension is not completely elucidated: both renal and extrarenal actions may be involved. The renal site of action is the proximal part of the distal tubule and the ascending part of Henle's loop. Sodium and chloride ions are excreted in approximately equivalent amounts. The increased delivery of sodium to the distal tubular exchange site results in increased potassium excretion and hypokalemia.

Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are obtained after 1 to 2 hours. Indapamide is concentrated in the erythrocytes and is 79% bound to plasma proteins and to erythrocytes.

It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility. Seventy per cent of a single oral dose is eliminated by the kidneys and 23 per cent by the gastrointestinal tract. Indapamide is metabolised to a marked degree, the unchanged product representing approximately 5 per cent of the total dose found in the urine during the 48 hours following administration. Elimination of indapamide from the plasma is biphasic with half–lives of 14 and 25 hours respectively.

Comparative Bioavailability

A double–blind, two–way, randomized, crossover bioavailability study was conducted in adult, healthy, male volunteers to evaluate the relative bioavailability of single oral doses (5 mg) of indapamide 2.5 mg tablets manufactured by Nutex Inc. and Lozide® 2.5 mg Tablets manufactured by Servier Canada Inc.

Summary Table of the Comparative Bioavailability Data
Indapamide (Dose: 2 x 2.5 mg) From Measured Data - Under Fasting Conditions

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu–Indapamide	Lozide®†	
AUC_T (ng•hr/mL)	3356 3437 (22)	3276 3375 (25)	102.4
AUC_I (ng•hr/mL)	3475 3564 (23)	3392 3505 (27)	102.5
C_{max} (ng/mL)	213 216 (17)	186 189 (19)	114.5
T_{max} (hr)*	1.26 (36)	2.04 (52)	
$t_{1/2}$ (hr)*	14.2 (17)	14.3 (17)	

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Lozide® is manufactured by Servier Canada Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

NU–INDAPAMIDE (indapamide) is indicated in the management of essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally NU–INDAPAMIDE, as other diuretics, is used as the initial agent in multiple drug regimens.

CONTRAINDICATIONS

Anuria, progressive and severe oliguria, hepatic coma. Known hypersensitivity to indapamide or to other sulphonamide derivatives.

WARNINGS

Electrolyte changes observed with indapamide become severe at doses above 2.5 mg per day. Therefore the maximum daily dose should not exceed this dose.

Hypokalemia may occur at all doses with consequent weakness, cramps, and cardiac dysrhythmias. Hypokalemia is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may be precipitated.

Hypokalemia occurs commonly with diuretics; electrolyte monitoring is essential particularly in patients who would be at increased risk from hypokalemia, such as patients with cardiac arrhythmias or those who are receiving concomitant cardiac glycosides.

Patients with renal insufficiency receiving NU–INDAPAMIDE (indapamide) should be carefully monitored. If increasing azotemia and oliguria occur during treatment, the diuretic should be discontinued.

Hyperuricemia may occur during administration of NU–INDAPAMIDE. Rarely gout has been reported. Blood uric acid levels should be monitored, particularly in patients with a history of gout, who should continue to receive appropriate treatment.

PRECAUTIONS

Patients receiving NU–INDAPAMIDE (indapamide) should be carefully observed and serum electrolytes monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatremia, hypochloremia and hypokalemia. Blood urea nitrogen, uric acid, and glucose levels should also be assessed during therapy. Hypokalemia, an ever present hazard with most diuretics will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake. The serum potassium should be determined at regular intervals and potassium supplementation instituted when indicated. (See WARNINGS.)

The signs of electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Special caution should be used in treating patients with severe hepatic disease since diuretics may induce metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide is given with other non–diuretic antihypertensive agents, the effects on blood pressure are additive.

Sulphonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. These possibilities should be kept in mind with the use of indapamide although no case has been reported to date.

Severe dermatological adverse reactions, some accompanied by systemic manifestations, have been rarely reported with the use of indapamide. In the majority of cases, the condition subsided within 14 days following discontinuation of indapamide therapy. (See ADVERSE REACTIONS.)

Caution should be observed when administering the drug to patients with severely impaired renal function, since the drug is excreted primarily by the renal route.

Although indapamide exerts minimal effect on glucose metabolism, insulin requirements may be affected in diabetics and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight 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 with signs of thyroid disturbance.

The antihypertensive effect of the drug may be enhanced in the patient postsympathectomy.

Use in Pregnancy

Since indapamide has not been studied in human pregnancy, the drug should not be given to pregnant women. The use in patients of child–bearing potential requires that the anticipated benefit be weighed against possible hazards.

Use in Nursing Mothers

It is not known whether indapamide is excreted in breast milk. NU–INDAPAMIDE should not be administered to nursing mothers. If use of the drug is deemed essential, the patient should stop nursing.

Use in Children

The safety and effectiveness of indapamide have not been established in children.

ADVERSE REACTIONS

The safety data presented under this section involves two different databases and was obtained at two different time periods. For the earliest database (indapamide 2.5 mg), consisting mainly of European studies performed before 1980, adverse events were collected with respect to a possible causal relationship to treatment, whereas for the most recent database (indapamide 1.25 mg), consisting exclusively of North-American studies, adverse events were collected irrespective of such a causal relationship. This explains why the overall incidence of adverse events at the 2.5 mg dose appears to be lower than at the 1.25 mg dose. (See below.)

Most adverse events for both dosages, 1.25 mg and 2.5 mg, have been mild or moderate.

The adverse reactions represent data from clinical studies involving a total of 992 patients given indapamide 2.5 mg: 349 patients from 4 placebo controlled studies treated for 8 to 12 weeks; 356 patients from 6 active controlled studies treated for 6 up to more than 52 weeks; 287 patients from 4 uncontrolled studies treated for 6 up to 40 weeks.

The overall rate of adverse events, with respect to a possible causal relationship to the drug, was 29% and discontinuation of therapy due to adverse events was required in 5.6% of patients.

The most severe and common adverse event is the electrolyte imbalance. Electrolyte changes reported include hypokalemia (14.2%; requiring potassium supplementation 6%; with clinical symptoms 1.2%), hypochloremia (9.4%) and hyponatremia (3.1%).

The other changes observed in laboratory parameters are minor and infrequent: elevation in blood uric acid (8.6%), blood glucose (6.0%), BUN (5.7%) and blood creatinine (3.6%).

The most frequent adverse events (incidence $\geq$1%) reported for patients treated with indapamide 2.5 mg were: headache (3.4%), vertigo (2.2%), dizziness (1.9%), asthenia (1.7%) and muscle cramps (1.2%).

All other adverse events occurred at an incidence of less than 1% and included by body system:

CENTRAL NERVOUS

Drowsiness, sleepiness, insomnia, weakness, lethargy and visual disturbance.

GASTROINTESTINAL

Nausea, anorexia, dryness of mouth, gastralgia, vomiting, diarrhea and constipation.

MUSCULOSKELETAL

Joint pain, back pain and weakness of legs.

CARDIOVASCULAR

Orthostatic hypotension, tachycardia and ECG changes (non–specific ST-T change, U waves, left ventricular strain).

UROGENITAL

Impotence, modification of libido and polyuria.

DERMATOLOGICAL

Rash and pruritus.

ENDOCRINE

Gout.

OTHER

Tinnitus, malaise, fainting and sweat.

In placebo-controlled studies involving 306 patients given indapamide 1.25 mg and 319 given placebo for up to eight weeks, the overall incidence of adverse events, irrespective of causal relationship, was about 50% in both indapamide and placebo groups. In the indapamide 1.25 mg group, 4.2% of patients discontinued treatment because of adverse events.

In these studies, 20% of patients treated with indapamide 1.25 mg had at least one potassium value below 3.4 mEq/L.

The most frequently reported adverse events (incidence ≥1%) in the indapamide 1.25 mg group were: headache (17%), infection (12%), pain (8%), dizziness (7%), back pain (5%), rhinitis (5%), asthenia (4%), dyspepsia (4%), flu syndrome (3%), hypertonia (3%), sinusitis (3%), chest pain (2%), constipation (2%), cough (2%), diarrhea (2%), edema (2%), nausea (2%), pharyngitis (2%), conjunctivitis (1%), nervousness (1%) and ECG abnormalities (non-specific ST-T changes (7%), sinus bradycardia (3%), arrhythmia (2%) or tachycardia (2%)).

All other clinical adverse events occurred at an incidence of less than 1%. These are the following:

CENTRAL NERVOUS

Agitation, amnesia, anxiety, ataxia, coordination abnormality, depression, dream abnormality, hyperesthesia, insomnia, migraine, paresthesia, somnolence, twitching and vertigo.

GASTROINTESTINAL

Increased appetite, dry mouth, GI carcinoma, GI disorders, duodenitis, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, oral moniliasis, proctitis, rectal disorders, rectal hemorrhoids, stomatitis, tooth disorders and vomiting.

MUSCULOSKELETAL

Arthralgia, arthritis, bone disorders, joint disorders, bone fracture, bone pain, chondrodystrophy, myalgia, myasthenia and myopathy.

CARDIOVASCULAR

Angina pectoris, bundle branch block, ventricular extrasystoles, atrial fibrillation, atrial flutter, hypertension, postural hypotension, palpitations, syncope, supraventricular tachycardia and vasodilation.

UROGENITAL

Dysmenorrhea, dysuria, impotence, urinary tract infection, nocturia, oliguria, urinary frequency or urgency, renal pain or calculus, prostate disorders and vaginitis.

RESPIRATORY

Bronchitis, dyspnea, laryngitis, lung disorder and sputum increase.

DERMATOLOGICAL

Acne, application site reaction, exfoliative dermatitis, nail disorder, skin nodule, rash, bullous eruption and sweat.

METABOLIC AND NUTRITIONAL

Diabetes mellitus and gout.

SPECIAL SENSES

Amblyopia, ear disorders, ear pain, otitis, photophobia, taste perversion, tinnitus and vision abnormality.

OTHER

Thyroid disorder, ecchymosis, allergic reaction, edema face, fever, hernia, malaise and monilia.

POSTMARKETING EXPERIENCE

Among the less common suspected adverse reactions reported, the following, which are not included elsewhere in the Product Monograph, have been published in the medical literature and/or are classified as serious or potentially serious: Stevens-Johnson syndrome, bullous eruption, photosensitivity with bullae, erythroderma, purpura, epidermal necrolysis, erythema multiforme, angioedema, cataract, acute myopia, optic neuritis, ventricular arrhythmia, torsades de point, stroke, acute hypersensitivity reaction leading to interstitial nephritis and renal failure, anemia, agranulocytosis, metabolic alkalosis, hyperosmolar coma, dehydration, hepatitis, pancreatitis, lithium toxicity, rhabdomyolysis, vasculitis, fever.

One case of synergetic effect of clofibrate with indapamide leading to hyponatremia, hypokalemia, hypoosmolarity, nausea and progressive loss of consciousness.

Relationship with the administration of indapamide has not been proved in all cases.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

There have been no reports of overdosage. Based on the pharmacological activities of NU–INDAPAMIDE (indapamide), overdosage may lead to excessive diuresis with electrolyte depletion. In cirrhotic patients, overdosage might precipitate hepatic coma.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug. Induce emesis or perform gastric lavage. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

DOSAGE AND ADMINISTRATION

One 1.25 mg tablet per day taken in the morning as a single dose. If the response is not satisfactory after 4 to 8 weeks, the dose may be increased to a maximum of 2.5 mg as a single dose taken in the morning. If the antihypertensive response to indapamide is insufficient, an increase in dosage is not recommended. (See WARNINGS.)

Instead a non–diuretic antihypertensive agent should be added to the drug regimen. Alternatively, if in the opinion of the physician, an important diuretic effect is desirable for the

patient's control, a different diuretic which allows for dose titration could be tried instead of indapamide.

PHARMACEUTICAL INFORMATION

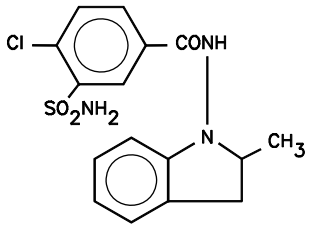
Drug Substance

Common Name: Indapamide

Chemical Names: 1) Benzamide, 3-(aminosulfonyl)-4-chloro-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)-;

2) 4-Chloro-*N*-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide.

Structural Formula:



Molecular Formula: $C_{16}H_{16}ClN_30_3S$

Molecular Weight: 365.83

Description: A white to off–white crystalline lipophilic powder soluble in methanol, ethanol, acetic acid, and ethyl acetate, very slightly soluble in ether, chloroform, and benzene, and practically insoluble in water.

Composition

NU–INDAPAMIDE (indapamide) 1.25 mg and 2.5 mg tablets contain 1.25 mg and 2.5 mg indapamide, respectively, along with the following non–medicinal ingredients: croscarmellose sodium, hydroxyethyl cellulose, lactose, magnesium stearate, polyethylene glycol, titanium dioxide. The 1.25 mg tablets also contain FD&C Yellow #6 Aluminum Lake 40%, D&C Yellow #10 Aluminum Lake 14-18%, and the 2.5 mg tablets also contain D&C Red #30 Aluminum Lake 30%.

Stability and Storage Recommendations

Store at room temperature (15 - 30°C) in tightly–closed containers.

AVAILABILITY OF DOSAGE FORMS

Each orange, round, biconvex, film–coated tablet, engraved “1.25” on one side, contains 1.25 mg indapamide. Available in bottles of 30, 100, 250, 500 and 1000, and in unit dose packages of 30 and 100.

Each pink, round, biconvex, film–coated tablet, engraved “2.5” on one side, contains 2.5 mg indapamide. Available in bottles of 30, 100, 250, 500 and 1000, and in unit dose packages of 30 and 100.

PHARMACOLOGY

Indapamide is a non–thiazide sulphonamide derivative with an indole ring, possessing antihypertensive and diuretic properties.

Antihypertensive Action

In normal rats, cats and dogs, intravenous administration of 30 μg to 30 mg/kg failed to change blood pressure or heart rate. No change in cardiac output, heart rate, peripheral or pulmonary resistance was seen. In rats, oral doses of up to 100 mg/kg did not change blood pressure over a 96 hour measurement period.

In hypertensive animals, single oral doses of 1 to 10 mg/kg, p.o., of indapamide elicited antihypertensive activity as follows:

– in deoxycorticosterone acetate (DOCA)/saline hypertensive rats with unilateral nephrectomy, a single dose of 10 mg/kg indapamide produced a maximal fall in systolic blood pressure of 25 mmHg after 24 hours and the antihypertensive action lasted for 72 hours.

– similar results were observed in DOCA/saline rats without nephrectomy.

– higher doses up to 100 mg/kg produced only small increases in activity but the blood pressure reduction continued for longer than 1 day.

Following repeated oral administration of indapamide (1 mg/kg) or trichloromethiazide (3 mg/kg) to DOCA/saline nephrectomized rats for 14 days, mean systolic blood pressure fell more with indapamide (33 mmHg) than with trichloromethiazide (23 mmHg). One week after indapamide treatment ended, the blood pressure had only partially returned towards pre–treatment value.

In the renal hypertensive dog, indapamide, 5 mg/kg p.o., produced a maximal reduction (37 mmHg) in systolic blood pressure after 48 hours and an antihypertensive effect was still evident after 4 days.

Repeated administration of 0.5 mg/kg/day p.o. for 11 weeks prevented the onset of hypertension in DOCA/saline hypertensive rats with unilateral nephrectomy; the effect was still apparent 5 weeks after interrupting treatment.

Hypertensive response induced by norepinephrine, tyramine or sympathetic stimulation were markedly reduced by indapamide (10 mg/kg p.o.) in amyelinated or DOCA/saline hypertensive rats.

Indapamide (10^{-5} and 10^{-4}M) diminished vascular hyperreactivity to epinephrine, norepinephrine and angiotensin in isolated organ preparations. Indapamide (10^{-6}g/mL) inhibited vascular smooth muscle cell contractility.

In renal hypertensive dogs, blood pressure was reduced at a dose of 1 mg/kg i.v. and cardiac output showed an increase after 2 hours and a slight decrease over 24 hours.

Action on the Kidney

Diuretic activity has been studied in rats and dogs. The parameters were modified differently depending on the dose: the natriuretic and chloruretic activity was observed after doses of 0.1 to 0.3 mg/kg p.o. or i.v., while increased urinary output was seen at 1 mg/kg p.o. or i.v.; and significant increases in urinary potassium excretion were reported after doses of 3 to 10 mg/kg p.o.

Indapamide did not alter glomerular filtration rate or renal hemodynamics in dogs, suggesting that it acts directly on renal tubules. Studies of positive and negative free water clearance suggested

that diuresis may have resulted from inhibition of water, sodium, and chloride reabsorption in the proximal portion of the distal tubule of the nephron.

TOXICOLOGY

Acute Toxicity (LD_{50})

Route of Admin.	Species	No. Animals	LD_{50} (mg/kg) 48 hours	LD_{50} (mg/kg) 10 days
Oral	Mice	10M 10F	>3000 (48 hr and 10 days)	
	Rats	10M 10F		
	Guinea-pigs	4M 4F		
Intra-venous	Mice	10M 10F	577 (538-618) 635 (589-684)	idem 48 hr 611 (575-648)
	Rats	10M 10F	440 (412-470) 394 (368-421)	433 (404-463) idem 48 hr
	Guinea-pigs	4M 4F	358 (312-409) 315 (249-397)	272 (176-421) 285 (239-341)

Signs of Toxicity

Piloerection, bradypnea, hypotonia, diminished motor activity, hypersensitivity, mydriasis, and vasodilation at parenteral doses greater than 400 mg/kg.

Indapamide administered with hydralazine, methyldopa or propranolol did not modify the oral LD_{50} of the other anti–hypertensive agents.

Subacute Toxicity

4–week oral toxicity study in rats (SPF/CFY strain):

Rats (5M, 5F/group) received indapamide once daily, 7 days a week for 4 weeks at 50, 100 and 200 mg/kg. The findings were: a dose–related increase in food consumption by females at 100 and 200 mg/kg, reduced body weight gain in males on high dose during the first two weeks and slight reduction in females at 200 mg/kg; increased number and prominence of foci of dystrophic mineralization at the cortico–medullary junction in 5/5 F at 200 mg/kg, considered to be due to increased urinary output.

Chronic Toxicity

6–month oral toxicity study in beagle dogs:

Dogs (3M, 3F/group) were treated with 0, 2, 20, 200 mg/kg doses, once daily, 7 days a week for 6 months. The drug related findings were: food intake significantly reduced in males at 20 and 200 mg/kg and in females at 200 mg/kg. Weight gain was significantly reduced in males at the 200 mg/kg dose.

At 200 mg/kg hypothermia, increased susceptibility to injuries and infections and increased urinary output were observed.

High neutrophil and low lymphocyte counts in all drug-treated females at week 13, persisting in the 200 mg/kg group. High reticulocyte count was also noted.

Elevation of cholesterol and blood glucose, reduction of Na, K, Cl and Mg at week 13 in the high dose group with persistence of the glucose abnormalities.

Significantly increased weight of liver and kidneys at 200 mg/kg and of adrenals at 20 and 200 mg/kg were seen. Sinusoidal congestion with central zone degeneration in the liver of one male of the 200 mg/kg group was noted. Slight congestion of the adrenals was also noted in 3 dosed animals.

52–week oral toxicity study in rats (SD/CR Strain):

Groups of 40 males and 40 females received indapamide at doses of 0, 1, 10 or 100 mg/kg once daily, 7 days a week for 52 weeks.

The findings were as follows:

Growth rates of treated males declined significantly during the first 6 weeks but terminal weights were comparable with controls.

Significant increases of plasma urea levels (still within the normal range) and of serum uric acid levels in males receiving the highest dose.

In females at high dose, significant weight increase of liver, kidneys and uterus and slight increase of adrenals were noted. Dose–related dystrophic mineralization at the cortico–medullary junction of kidneys of all drug–treated groups, particularly in females. Six females (2 at each dose) showing these changes died before the termination of the study. Calculi in the bladder of 3 females and bladder papilloma in one at 100 mg/kg dose.

56–week oral toxicity study in beagle dogs:

Groups of 4 males and 4 females were treated once daily, 7 days a week with 0, 1, 10 and 100 mg/kg of indapamide (the highest dose was reduced to 50 mg/kg on day 86).

The findings were as follows:

Excessive diuresis in all dosed animals. Reduction of body weight gain marked at 100 mg/kg; slight at 10 mg/kg. Reduction of food consumption in high dose group. ECG changes (alteration of ventricular repolarisation) in 4 animals of the high dose group, 3 at week 11 and 1 at week 26. One of the 2 surviving females in the high dose group had a serum potassium level of 2.6 mEq/L.

Hemoconcentration during the first half period of treatment. Abnormally low serum potassium levels after week 6 at middle and high doses and after week 17 in some low dose animals. High serum cholesterol levels at week 26 in the high dose group.

In high dose groups, about 50% weight reduction of uterus or prostate and ovaries, and weight increase of kidney and adrenals were seen. Replacement of cardiac muscle by adipose tissue in 4/8 animals at high dose. Apparent enlargement of adrenal cortex in 3/4 dogs in the high dose group. Flex dystrophic mineralization observed in renal medulla in all groups, including controls.

Carcinogenicity

Indapamide was administered to 3 groups of 60 male and 60 female Charles River CD1 rats and mice at dietary levels of 10, 30 and 100 mg/kg/day for 104 and 91 weeks respectively. A fourth group served as the negative control group. Both strains are susceptible to known carcinogens.

In both species the incidence of nodules and masses observed at necropsy was comparable between the treated and control groups. Drug related changes in the kidney (tubular nephrosis and mineralization of parenchyma) were seen in rats. Increased liver cytoplasmic vacuolization was seen in mice.

Under the conditions of testing, indapamide was not tumorigenic.

Teratogenicity

The teratogenic potential of indapamide was investigated in 3 animal species: mice, rats and rabbits.

In mice CD/SPF (groups of 30 females), indapamide administered at doses of 0, 5 and 20 mg/kg/day p.o., 6 days a week, from the day of mating and throughout pregnancy did not induce abortions or increase the percentage of deaths of the litters. No apparent teratogenic effect was noted.

In rats SD/SPF, no embryotoxicity was noted in the fetuses of 3 females receiving a daily dose of 250 mg/kg p.o. from the 9th to the 16th day of gestation.

In rats SD/SPF (groups of 60 females) receiving from the day of mating until the end of pregnancy 0, 10 and 30 mg/kg/day p.o., 6 days a week, indapamide had no effect on the abortion rate, the mean number of fetuses per litter or the incidence of abnormalities.

In rats CR/CD (groups of 20 females) receiving 0, 1, 25 or 125 mg/kg, once daily from days 6 to 15 of gestation, no adverse effects were reported on abortion rate, implantation rate, mean litter

size or fetal weight or fetal mortality. Slightly higher incidence of visceral abnormalities (thin walled heart, hydronephrosis) in treated animals (19-26% versus 17% in controls).

In the domestic rabbit (groups of 15 females) receiving 0, 1, 5, 10 and 50 mg/kg/day p.o., once daily, 6 days a week, from the 6th to 18th day of gestation, increased resorption rates were seen at 50 mg/kg. No apparent teratogenic effect was noted.

In the New–Zealand white rabbit (groups of 13 females) receiving 0, 5, 30 and 180 mg/kg/day p.o., once daily from days 6 to 18 of gestation, reduction in food consumption and weight gain at 180 mg/kg during the first 4 days of dosing were observed. Total loss of litters occurred in 2 animals at high dose. In the other animals, abortion rate and litter size were unchanged. Incidence of major malformations and minor abnormalities were comparable for all groups and considered to be within the Laboratory standard range.

Fertility and Reproduction

Three generation tests, Wistar rats (SPF Strain):

Indapamide was administered at 0, 0.5, 2.5 and 25 mg/kg p.o., once daily to 20 males/group for 70 days before mating and 15 days after, and to 10 females/ group for 8 days before mating up to 30 days post-mating. Findings were as follows:

Reproductive performance was not changed. No changes in mean weight, mean number of fetuses, the incidence of malformations or the death rate among neonates were observed.

Behaviour and reproductive performance of offspring were unaffected but the death rate of neonates (F_2 generation) was adversely affected: 35% at low doses and 47% at the high dose versus 16% in controls (the lack of milk formation in the mothers may have been the cause).

No adverse effects on the F_3 generation pups were observed.

REFERENCES

1. Acchiardo SR, Skoutakis VA. Clinical efficacy, safety and pharmacokinetics of indapamide in renal impairment. Am Heart J 1983; 106 (Suppl): 239-44.

2. Ames RP, Griffing E, Marbury T, et al. Effectiveness of indapamide versus enalapril as second-step therapy of systemic hypertension. Am J Cardiol 1992; 69: 267-70.

3. Brennan L, Wu MJ, Laquer UJ. A multicenter study of indapamide in hypertensive patients with impaired renal function. Clin Ther 1982; 5: 121-8.

4. Clarke RJ. Indapamide: a diuretic of choice for the treatment of hypertension? Am J Med Sci 1991; 301 (3): 215-20.

5. Expert Committee of the Canadian Diabetes Advisory Board. Clinical practice guidelines for treatment of diabetes mellitus. Can Med Assoc J 1992; 147: 697-712.

6. Ferdinand K, Flamenbaum W, Hall WD et al. Lower dose indapamide therapy in the treatment of patients with mild to moderate hypertension. Am J Hypertens 1993; 6 (5 part 2): 121A.

7. Harrower ADB, McFarlane G, Donnelly T, Gray CE. Effect of indapamide on blood pressure and glucose tolerance in non-insulin-dependent diabetes. Hypertension 1985; 7 (Suppl II): 161-3.

8. Kocijancic M, Dimkovic S. Antihypertensive effect of indapamide given in conjunction with captopril in severe hypertension. Curr Med Res Opin 1986; 10: 313-8.

9. Leenen FHH, Smith DL, Boer WH, Marquez-Julio A. Diuretic and cardiovascular effects of indapamide in hypertensive subjects: A dose-response curve. Curr Med Res Opin 1983; 8 (Suppl 3): 47-52.

10. Leenen FHH, Smith DL, Farkas RM et al. Cardiovascular effects of indapamide in hypertensive patients with or without renal failure. Am J Med 1988; 84 (Suppl 1B): 76-85.

11. Leonetti G, Rappelli A, Salvetti A et al. Long-term effects of indapamide: final results of a two-year Italian multicenter study in systemic hypertension. Am J Cardiol 1990; 65: 67H-71H.

12. Levine B. Treatment of hypertension in the elderly. Clin Ther 1994; 16 (5): 732-51.

13. Newstead CG, Moore RH, Barnes AJ. Interstitial nephritis associated with indapamide. Br Med J 1990; 300: 1344.

14. Ocon J, Mora J. Twenty-four-hour blood pressure monitoring and effects of indapamide. Am J Cardiol 1990; 65: 58H-61H.

15. Plante GE, Dessurault DL. Hypertension in elderly patients. A comparative study between indapamide and hydrochlorothiazide. Am J Med 1988; 84 (Suppl 1B): 98-103.

16. Plante GE, Massry SC, et al. Comparison between the effects of indapamide and hydrochlorothiazide on creatinine clearance in patients with impaired renal function and hypertension. Am J Nephrol 1995; 15: 251-5.

17. Raggi U, Palumbo P, Bevilacqua M et al. Indapamide in the treatment of hypertension in non-insulin-dependent diabetes. Hypertension 1985; 7 (Suppl II): 157-60.

18. Soltero I, Fuenmayor I, Colmenares A, et al. Comparative study of indapamide, beta-blockers, and diet. Curr Ther Res 1989; 46 (2): 327-35.

19. Stricker BHCh, Biriell C. Skin reactions and fever with indapamide. Br Med J 1987; 295:1313-14.

20. Van Hee W, Thomas J, Brems H. Indapamide in the treatment of essential arterial hypertension in the elderly. Postgrad Med J 1981; 57 (suppl 2): 29-33.

21. Waal-Manning HJ, Doesburg RMN, Spears GFS. Indapamide in hypertension. N Z Med J 1987; 100: 251-2.

22. Weiss R, Toth P, Miller E, et al. Clinical efficacy and safety of lower-dose indapamide therapy in the treatment of patients with mild to moderate hypertension. Am J Ther 1994; 1: 58-64.