PRODUCT MONOGRAPH

RIVA-INDAPAMIDE
(Indapamide USP)

1.25 and 2.5 mg Tablets

Diuretic / Antihypertensive Agent

Laboratoire Riva Inc.
660 Boul. Industriel
Blainville PQ
J7C 3V4

Date of Preparation
February 19, 2003

Control # 082691

PRODUCT MONOGRAPH

RIVA–INDAPAMIDE

(Indapamide tablets USP)

THERAPEUTIC CLASSIFICATION

Diuretic/Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

RIVA–INDAPAMIDE (Indapamide tablets USP) is classified as a diuretic antihypertensive agent. The mechanism of action of indapamide in the management of hypertension is not thoroughly understood. Both renal and extrarenal actions may be involved. The mechanism site in the kidney is the proximal portion 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 quickly and thoroughly absorbed following oral administration. Peak serum concentrations are attained after 1–2 hours. The highest concentration of indapamide is found in the erythrocytes. Indapamide is 79% bound to plasma proteins and to erythrocytes.

Indapamide is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility. 70% of a single oral dose is eliminated renally and 23% by the gastrointestinal tract. Indapamide is extensively metabolised with only 5% of the total dose appearing in the urine as unchanged drug 48 hours after administration. Indapamide elimination from the plasma is biphasic with half–lives of 14 and 25 hours respectively.

A comparative two–way, single–dose bioavailability study was performed between RIVA–INDAPAMIDE (Indapamide tablets USP) 2.5 mg Tablets and LOZIDE® (Indapamide tablets USP) 2.5 mg Tablets. The pharmacokinetic plasma data calculated for the two formulations are tabulated below:

Parameter	Geometric Mean Arithmetic Mean (C.V.) RIVA–INDAPAMIDE (2 x 2.5 mg)	LOZIDE®** (2 x 2.5 mg)	Percentage of LOZIDE®
AUC_T (ng•h/mL)	3374 3545 (33)	3237 3348 (27)	104
AUC_I (ng•h/mL)	3945 4106 (30)	3774 3875 (24)	104
C_{max} (ng/mL)	193 205 (41)	176 181 (23)	111
T_{max}* (h)	3.25 (98.2)	2.46 (67.8)	—
$T_{1/2}$* (h)	18.25 (29.9)	15.34 (16.8)	—

*These are the arithmetic means (C.V.).
** LOZIDE® 2.5 mg Tablets (Servier Canada Inc.), Canada.

INDICATIONS AND CLINICAL USE

RIVA–INDAPAMIDE (Indapamide tablets USP) is indicated in the management of essential hypertension. It can be used as a sole therapeutic agent in the treatment of mild to moderate hypertension. Usually indapamide, like other diuretics, is used as the first medication in multiple drug regimens.

CONTRAINDICATIONS

RIVA–INDAPAMIDE (Indapamide tablets USP) is contraindicated in anuria, progressive and severe oliguria and hepatic coma. It is also contraindicated in patients with a known hypersensitivity to indapamide or other sulphonamide derivatives.

WARNINGS

Alterations in electrolytes after indapamide administration become severe at doses higher than 2.5 mg/day. Thus, the daily maximum dose should not exceed 2.5 mg.

Hypokalemia can occur with all doses with resultant 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 RIVA–INDAPAMIDE (Indapamide tablets USP) should be kept under close supervision. If increasing azotemia and oliguria occur during therapy, treatment with diuretic should be discontinued.

Hyperuricemia could occur with RIVA–INDAPAMIDE treatment. Gout has occurred rarely. 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 RIVA–INDAPAMIDE (Indapamide tablets USP) 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 use and with inadequate electrolyte intake. Serum potassium levels should be measured regularly and potassium supplementation initiated when necessary (see WARNINGS).

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

Special care should be taken when treating patients with severe liver 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 simultaneous administration of other antihypertensives.

When indapamide is taken with other non–diuretic antihypertensives, 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 responses, some accompanied by systemic manifestations, have been rarely reported with indapamide therapy. In the majority of cases, the condition subsided within 14 days following withdrawal of indapamide (see ADVERSE REACTIONS).

When giving indapamide to patients with severe renal impairment, caution must be exercised because the drug is excreted mainly by the kidney.

Although indapamide exerts minimal effect on glucose metabolism, insulin requirements may be affected in diabetics and hyperglycaemia 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 without signs of thyroid disturbance.

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

Use in Pregnancy:

RIVA–INDAPAMIDE should not be administered to pregnant women because indapamide has not been studied in human pregnancy. RIVA–INDAPAMIDE should be used in patients of child–bearing potential only when the expected benefits outweigh the potential risks.

Use in Nursing Mothers:

It is not known whether indapamide is excreted into breast milk, thus RIVA–INDAPAMIDE should not be taken by nursing mothers, or, if indapamide therapy is necessary, the patient should cease from nursing.

Use in Children:

The safe and effective use of indapamide in children has not been determined.

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 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, diarrhoea 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 pruritis.

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%), diarrhoea (2%), oedema (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, co-ordination abnormality, depression, dream abnormality, hyperesthesia, insomnia, migraine, paresthesia, somnolence, twitching and vertigo.

Gastrointestinal: increased appetite, dry mouth, GI carcinoma, GI disorders, duodenitis, dysphagia, oesophagitis, flatulence, gastritis, gastro-enteritis, oral moniliasis, proctitis, rectal disorders, rectal haemorrhoids, 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 vasodilatation.

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, oedema 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 pointe, stroke, acute hypersensitivity reaction leading to interstitial nephritis and renal failure, anaemia, 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

There have not been any reported cases of overdosage to date. Based on the pharmacological action of indapamide, overdosage could result in excessive diuresis with electrolyte depletion. In cirrhotic patients, overdosage might precipitate hepatic coma.

There is no specific antidote for indapamide overdose. Treatment should be symptomatic and supportive. If overdose is suspected, the drug should be withdrawn at once. Emesis should be induced or gastric lavage performed. Dehydration, electrolyte imbalance, hepatic coma and hypotension should be treated 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 RIVA–INDAPAMIDE (Indapamide tablets USP) 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.

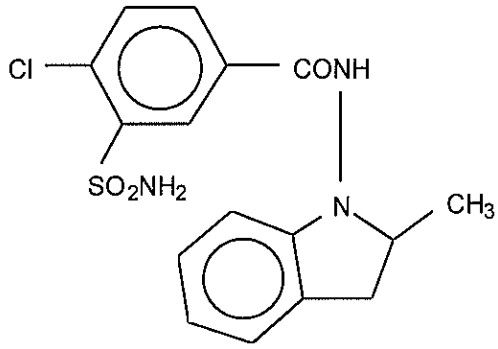
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Indapamide

Chemical Name: 4-Chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide

Structural Formula:



Molecular Formula: $C_{16}H_{16}ClN_3O_3S$ Molecular Weight: 365.83

Description: White to off–white crystalline powder. Pk_a value is 9.20. Melts between 167°–170°C. Soluble in methanol, alcohol, acetonitrile, glacial acetic acid and in ethyl acetate. Very slightly soluble in ether and in chloroform and practically insoluble in water.

STABILITY AND STORAGE RECOMMENDATIONS: Store bottles between 15°–30°C. Store units doses boxes between 15°–25°C and protect from high humidity.

COMPOSITION:

Each RIVA–INDAPAMIDE (Indapamide tablets USP) 2.5 mg tablet contains indapamide 2.5 mg, and non-medicinal ingredients: lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate, sodium lauryl sulfate, sucrose, acacia, talc, colloidal silicon dioxide, carnauba wax, white wax, titanium dioxide, D&C red No. 30 aluminium lake, FD&C yellow No. 6 aluminium lake, povidone and sodium benzoate.

Each RIVA–INDAPAMIDE (Indapamide tablets USP) 1.25 mg tablet contains indapamide 1.25 mg, and non-medicinal ingredients: lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate, sodium lauryl sulfate, sucrose, acacia, talc, colloidal silicon dioxide, carnauba wax, white wax, titanium dioxide, D&C red No. 30 aluminium lake, povidone and sodium benzoate.

AVAILABILITY OF DOSAGE FORMS

RIVA–INDAPAMIDE (Indapamide tablets USP). Each pink, round, biconvex, coated tablet, engraved with a "P" logo on one side and "IN 2.5" on the other side, contains: indapamide 2.5 mg. Compliance packs of 30. Bottles of 100.

RIVA–INDAPAMIDE (Indapamide tablets USP). Each orange, round, biconvex, coated tablet, engraved "Riva" on one side and "IN 1.25" on the other side, contains: indapamide 1.25 mg. Compliance packs of 30. Bottles of 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 effect in cardiac output, heart rate, peripheral or pulmonary resistance was observed. In rats oral doses of up to 100 mg/kg did not affect blood pressure over a 96 hour measurement period.

In hypertensive animals, single oral doses of 1–10 mg/kg, p.o., of indapamide caused antihypertensive responses as follows;

- In desoxycorticosterone acetate (DOCA)/saline hypertensive rats with unilateral nephrectomy, a single 10 mg/kg dose of 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 resulted in only minor increases in activity, however the blood pressure reduction continued for longer than 1 day.

Following repeated oral administration of indapamide (1 mg/kg) or trichlormethiazide (3 mg/kg) to DOCA/saline nephrectomized rats for 14 days, mean systolic blood pressure fell more with indapamide (33 mm Hg) than with trichlormethiazide (23 mm Hg). One week after indapamide treatment, 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 mm Hg) 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 of 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 was markedly reduced by indapamide (10 mg/kg p.o.) in amyelinated or DOCA/saline hypertensive rats.

Indapamide (10^{-5} and 10^{-4} M) decreased vascular hyperactivity 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 decreased by a 1 mg/kg i.v. dose and cardiac output showed an increase after 2 hours and a slight decrease over 24 hours.

Action on the Kidney

Diuretic activity has been investigated in rats and dogs. Each parameter was altered in a different way according to the dose: the natriuretic and chloruretic effects were seen after doses of 0.1 to 0.3 mg/kg p.o. or i.v., while increased urinary output was observed at 1 mg/kg p.o. or i.v; and significant increases in urinary potassium excretion were reported at doses of 3 to 10 mg/kg p.o.

Indapamide did not affect glomerular filtration rate or renal hemodynamics in dogs, indicating that its action is directly on the renal tubules. Investigations 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	Animals	No. Animals	LD_{50} (mg/kg) 48 hours	LD_{50} (mg/kg) 10 days
PO	mice	10 M 10 F	>3000 (48 hr and 10 d.)	
	rats	10 M 10 F		
	guinea-pigs	4 M 4 F		
IV	mice	10 M 10 F	577 (538-618) 635 (589-684)	idem 48 hr 611 (575-648)
	rats	10 M 10 F	440 (412-470) 394 (368-421)	433 (404-463) idem 48 hr
	guinea-pigs	4 M 4 F	358 (312-409) 315 (249-397)	272 (176-421) 285 (239-341)

Signs of Toxicity: Piloerection, bradypnea, hypotonia, diminished motor activity, hypersensitivity, mydriasis, and vasodilatation 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

Four-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: 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 cortico-medullary function in 5/5 F at 200 mg/kg, considered to be due to increased urinary output.

Chronic Toxicity:

Six–month oral toxicity study in beagle dogs: Dogs (3M, 3F/group) were given 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 significantly reduced in males at 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 count 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, reductions of Na, K, Cl and Mg at week 13 in 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 adrenals in 3 dosed animals.

Fifty-two week oral toxicity study was conducted 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: 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.

Fifty-six week oral toxicity study in beagle dogs: Groups of 4 males and 4 females 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: 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 (alterations 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 of 2.6 mEq/L.

Hemoconcentration during the first half period of treatment. Abnormally low serum K 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 out of 8 animals at the high dose group. Apparent enlargement of adrenal cortex in 3 out of 4 dogs in the high dose group. Flex dystrophic mineralization observed in renal medulla in all groups, including controls.

Carcinogenicity Studies:

Indapamide was administered to 3 groups of 60 male and 60 female Charles River CD-1 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 vacuolisation was seen in mice.

Under the conditions of testing, indapamide was not tumorigenic.

Reproduction and Teratology:

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 percentage of deaths of the litters. No apparent teratogenic effect was noted.

- In rats SD/SPF: no embryotoxicity was noted in the foetuses 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, 30 mg/kg/day p.o., 6 days a week, indapamide had no effect on the abortion rate, the mean number of foetuses 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 foetal weight, or foetal mortality. Slightly higher incidence of visceral abnormalities (thin–walled heart, hydronephrosis) in treated animals (19-26% vs 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 6^{th} to 18^{th} day of gestation increased resorption rate was 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 showed reduction in food consumption and weight gain at 180 mg/kg during the first 4 days of dosing. 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.

Three generation tests were performed in 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 foetuses, the incidence of malformations or the death rate among neonates were observed.

Behaviour and reproductive performance of off-spring were unaffected but the death rate of neonates (F_2 generation) was adversely affected: 35% at low doses and 47% at the high dose vs 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. Abbou C-B. The efficacy and tolerance of indapamide in essential hypertension: a multi-centre study in 981 patients. Curr Med Res Opin 1985; 9: 494-9.

2. Burke TJ, Nobles EM, Wolf PS, Erickson AL. Effect of indapamide on volume-dependent hypertension, renal haemodynamics, solute excretion and proximal nephron fractional reabsorption in the dog. Curr Med Res Opin 1983; 8: 25-37.

3. Campbell DB. The possible mode of action of indapamide: a review. Curr Med Res Opin 1983; 8: 9-24.

4. Campbell DB, Moore RA. The pharmacology and clinical pharmacology of indapamide. Postgrad Med J 1981; 57: 7-17.

5. Campbell DB, Taylor AR, Moore R. Observations on the pharmacokinetics of indapamide in man. Br J Clin Pharmacol 1976; 3: 971P.

6. Caruso FS, Szabadi RR, Vukovich RA. Pharmacokinetics and clinical pharmacology of indapamide. Am Heart J 1983; 106: 212-20.

7. Chaffman M, Heel RC, Brogden RN, et al. Indapamide. A review of its pharmacodynamic properties and therapeutic efficacy in hypertension. Drugs 1984; 28: 189-235.

8. Gensini G, Esente P, Giambartolomei A. A systemic hemodynamic evaluation of indapamide. Clin Ther 1983; 5: 475-82.

9. Hicks PE. The effects of long term oral treatment with indapamide on the development of DOCA-salt hypertension in rats: vascular reactivity studies. Clin Exp Hypertension 1979; 1: 713-31.

10. Klunk LJ, Ringel S, Neiss ES. The disposition of ^{14}C-indapamide in man. J Clin Pharmacol 1983; 23: 377-84.

11. Kyncl J, Oheim K, Seki T, Solles A. Antihypertensive action of indapamide. Comparative studies in several experimental models. Arzneim Forsch 1975; 25: 1491-5.

12. Mroczek WJ. Indapamide: clinical pharmacology, therapeutic efficacy in hypertension, and adverse effects. Pharmacotherapy 1983; 3: 61-7.

13. Noble RE, Webb EL, Godfrey JC, et al. Indapamide in the stepped-care treatment of obese hypertensive patients. Curr Med Res Opin 1983; 8: 93-104.

14. Perez-Stable E, Caralis PV. Thiazide-induced disturbances in carbohydrate, lipid, and potassium metabolism. Am Heart J 1983; 106: 245-51.

15. Pruss T, Wolf PS. Preclinical studies of indapamide, a new 2-methylindoline antihypertensive diuretic. Am Heart J 1983; 106: 208-11.

16. Uehara Y, Shirahase H, Nagata T, et al. Radical scavengers of indapamide in prostacyclin synthesis in rat smooth muscle cell. Hypertension 1990; 15: 216-24.

17. The Medical Letter Inc. Indapamide (Lozol) - A new antihypertensive agent and diuretic. Med Lett Drugs Ther 1984; 26: 17-8.

18. United States Food and Drug Administration Review and Evaluation of Preclinical Pharmacology and Toxicology Data for Lozide (Inadapamide tablets USP_, NDA #18-538: p.1-44.

19. United States Food and Drug Administration Medical Officer Review for Lozide (Inadapamide tablets USP_, NDA #18-538. August 11, 1980: p.1-64.

20. AHFS Drug Information 1995. American Society of Hospital Pharmacists Inc., Bethesda, MD, USA, 1995: 1786-9.

21. CPS 1995. Canadian Pharmaceutical Association, Ottawa, Ontario, Canada 1995: 730-1.

22. Product Monograph for Lozide® (Indapamide tablets USP)Tablets, Servier Canada Inc., Date of Preparation: August 4, 1995.

23. A Two–Way Single–Dose Bioavailability Study of Indapamide 2.5 mg Tablets in Normal Healthy Male Volunteers. Completed March 1992.

16. Uehara Y, Shirahase H, Nagata T, et al. Radical scavengers of indapamide in prostacyclin synthesis in rat smooth muscle cell. Hypertension 1990; 15: 216-24.

17. The Medical Letter Inc. Indapamide (Lozol) - A new antihypertensive agent and diuretic. Med Lett Drugs Ther 1984; 26: 17-8.

18. United States Food and Drug Administration Review and Evaluation of Preclinical Pharmacology and Toxicology Data for Lozide (Inadapamide tablets USP_, NDA #18-538: p.1-44.

19. United States Food and Drug Administration Medical Officer Review for Lozide (Inadapamide tablets USP_, NDA #18-538. August 11, 1980: p.1-64.

20. AHFS Drug Information 1995. American Society of Hospital Pharmacists Inc., Bethesda, MD, USA, 1995: 1786-9.

21. CPS 1995. Canadian Pharmaceutical Association, Ottawa, Ontario, Canada 1995: 730-1.

22. Product Monograph for Lozide® (Indapamide tablets USP)Tablets, Servier Canada Inc., Date of Preparation: August 4, 1995.

23. A Two–Way Single–Dose Bioavailability Study of Indapamide 2.5 mg Tablets in Normal Healthy Male Volunteers. Completed March 1992.