INDAPAMIDE TABLETS USP

DESCRIPTION
Indapamide is an oral antihypertensive diuretic. Its molecular formula is C_{26}H_{28}N_2O_2S, and it contains one sulfonamide moiety and a brain- and solvent-solute methylthiazide moiety. It differs chemically from the thiazides in that it does not possess the thiazide ring system and is derived from the benzothiazine group. The empirical formula of indapamide is C_{4}H_{8}N_2O_2S, and its molecular weight is 178.3. The compound is a white, odorless, tasteless, and soluble in aqueous solutions of strong bases. It is a white to yellow-white crystalline (tetragonal) powder.

Each tablet, for oral administration, contains indapamide 1.25 mg or 2.5 mg. In addition, each tablet contains the following inactive ingredients: FD C Yellow No. 6 (1.25 mg), hydroxypropyl methylcellulose, lactose, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY
Indapamide is the first in a new class of antihypertensive diuretics, the indolines. The oral administration of 2.5 mg (two 2.5 mg tablets) of indapamide to male subjects produced peak concentrations of approximately 115 ng/ml of the drug in blood within two 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 blood within two hours. In a 24-hour collection period, peak blood levels were reached by the expanded uterus, is properly traversed by evaluation of the leg bones and the use of support hose, use of diuretics to lower intravascular volume, the medical community, and proper treatment of 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 1.0, and the total plasma concentration and decreases to 3.51 at eight 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 excretion of 14C-labeled indapamide and metabolites averaged 55% of the administered dose during 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 reduced blood pressure and antihypertensive effects. Doses of 5 mg and 2.5 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, 0.81 and 0.76 mEq/l, respectively, was observed and uric acid increase by about 0.69 mEq/100 ml.

Indapamide administration in hypertension and edema are approximately equal to those obtained with conventional thiazide diuretics.

In hypertensive patients, daily doses of 1.25, 2.5 and 5 mg of indapamide have no appreciable cardiac inotropic or chronotropic effect. The drug decreases peripheral resistance, with little effect on renal blood flow. Changing signs of fluid or electrolyte imbalance, such as hypotension, electrolyte disturbances, and gastrointestinal disturbance. Electrolyte determinations are particularly important in patients who are vomiting excessively or receiving parenteral fluids. In patients not subject to electrolyte imbalance (including those with heart failure, kidney disease, and cirrhosis), and in patients on a salt-restricted diet.

The risk of hypotension secondary to diuresis and natriuresis is increased when larger doses are used, whereas diuretics are, in severe cirrhosis is present and during concomitant use of diuretics or ACTH.

Indapamide is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs.

Indapamide is also indicated for the treatment of salt and fluid retention associated with congestive heart failure.

Usages in Pregnancy: The routine use of diuretics in an otherwise healthy pregnancy is not recommended because it may cause fetal and/or neonatal death. Therefore, it is recommended that the use of these agents in the treatment of toxemia is avoided.

Edema during pregnancy may arise from pathological causes or from the pharmacological and mechanical consequences of pregnancy. The majority of cases of edema during pregnancy is due to pathological causes, just as it is in the absence of pregnancy (however, see PRECAUTIONS below). Dependent edema in normal pregnancy is not a true edema of pregnancy and disappears with delivery. However, edema is caused by these factors in the absence of cardiovascular disease, but which is associated with edema, including generalized edema in the majority of pregnant women with antihypertensive agents. Therefore, increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents. Increasing in pregnancy increases the risk of edema. In the presence of cardiovascular disease, there is an increased risk of edema in patients with antihypertensive agents.

2. Hypocorticism: Serum concentrations of cortisol are decreased due to corticotropin therapy and decreased due to corticotropin therapy. Thus, cortisol levels should be used as a guide of the response to therapy.

3. Renal Impairment: Indapamide, like the thiazides, should be used with caution in patients with severe renal disease. If renal function is necessary in patients receiving indapamide, it should therefore be monitored during treatment.

4. Impaired Hepatic Function: Indapamide, like the thiazide, should be used with caution in patients with impaired hepatic function or who have a diminished capacity to metabolize drugs.

5. Glucose Tolerance: The effects of indapamide on glucose tolerance in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.7 mg/100 ml 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.

6. Calcium Excretion: Calcium excretion is decreased by diuretics pharmacologically related to Indapamide. After six to eight weeks of indapamide 1.25 mg treatment in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Pretreatment with drugs pharmacologically related to Indapamide may in rare instances be associated with hypercalcemia and hypercalciuria. Hemolysis and electrolyte imbalance is essential, particularly in patients who will be at increased risk of renal impairment, such as renal failure, 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.

7. Interaction With Systemic Lupus Erythematosus: Patients have experienced exacerbation or activated systemic lupus erythematosus and this possibility should be considered with indapamide as well.

DRUG INTERACTIONS
1. Antihypertensive Agents: Indapamide may add to or potentiate the action of other antihypertensive drugs. In limited controlled trials that compared the effect of indapamide combined with others, the use was controlled by the other drugs administered alone, there was no notable change in the nature or frequency of adverse reactions associated with the combined therapy.

2. Lithium: See WARNINGS.

3. Post-Partum Hypertensive Patient: The antihypertensive effect of the drug may be enhanced in the post-partum hypertensive patient.

4. Nonphosphatase: Indapamide, like the thiazides, may decrease renin responsiveness to nonphosphatase, but this diminution is not sufficient to preclude effectiveness of the phosphatase-sensitive renin-angiotensin system.

CARCINOGENICITY, MUTAGENICITY, IMPAIRMENT OF FERTILITY: Both mouse and rat lifetime carcinogenicity studies were conducted. There was no significant difference in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy/Drug Interactions: Pregnancy Category B.

Reproduction studies have been performed in rats, mice and rabbits at doses up to 6.250 times the therapeutic human dose and have revealed no evidence of impaired fertility or harm to the fetus due to indapamide. Postnatal development in rats and mice was unaffected by pretreatment of parent animals during gestation. There are, however, no adequate and well-controlled studies in pregnant women. It is known to cross the placental barrier and appear in cord blood. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. There may be hazards associated with the use of this drug, especially during the first trimester. It is known to cross the placental barrier and appear in cord blood. Therefore, it is recommended that the use of these agents in the treatment of toxemia is avoided.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because most drugs are excreted in human milk, if use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS
Most of the adverse reactions have been mild and transient.

The adverse reactions listed in Table 3 are representative of the adverse reactions reported during the clinical studies and are generally those expected with diuretic therapy.

Indapamide TABLETS USP are indicated for the treatment of hypertension. If the patient's blood pressure is not controlled, a switch to higher doses or other antihypertensive agents may be necessary.

The adverse reactions listed in Table 3 are representative of the adverse reactions reported during the clinical studies and are generally those expected with diuretic therapy.
TABLE 1: Adverse Reactions from Studies of 1.25 mg
Incidence ≥ 5%  Incidence < 5%
BODY AS A WHOLE
Headache  Asthenia
Infection  Flu Syndrome
Pain  Abdominal Pain
Back Pain  Chest Pain
GASTROINTESTINAL SYSTEM
Constipation  Diarrhea
Dyspepsia  Nausea
Metabolic System  Peripheral Edema
Central Nervous System  Nervousness
Dizziness  Hypertonia
Respiratory System  Cough
Rhinitis  Pharyngitis
Sinusitis  Conjunctivitis
Special Senses

"OTHER"
All other adverse clinical reactions occurred at an incidence of <1%.
Approximately 4% of patients given indapamide 1.25 mg compared to 3% of the patients given placebo discontinued treatment in the trials of up to six weeks because of adverse reactions.
In controlled clinical trials of six to eight weeks in duration, 20% of patients receiving indapamide 1.25 mg, 61% of patients receiving indapamide 5.0 mg, and 100% of patients receiving indapamide 10.0 mg had at least one potassium value below 3.4 mEq/L. In the indapamide 1.25 mg group, about 40% of those patients who reported hypokalemia as a laboratory adverse event returned to normal serum potassium values without intervention. Hypokalemia with concurrent clinical signs or symptoms occurred in 2% of patients receiving indapamide 1.25 mg.

FUNCTIONS FROM STUDIES OF 2.5 mg and 5.0 mg
Incidence ≥ 5%  Incidence < 5%
Central Nervous System
Dizziness  Fatigue, weakness, loss of energy, lethargy, tiredness, or malaise
Muscle cramps or spasm, or numbness of the extremities
Nervousness, tension, irritability, agitation
Gastrointestinal System
Light-headedness  Drowsiness
Vertigo  Insomnia
Depression  Blurred Vision
Cardiovascular System
Orthostatic hypotension  Premature ventricular contractions
Irregular heart beat  Palpitations
Frequency of urination  Nocturia
Polyuria

OVDOSAGE
Symptoms of overdose include nausea, vomiting, weakness, gastrointestinal disorders and disturbances of electrolyte balance. In severe instances, hypotension and depressed respiration may be observed. If this occurs, support of respiration and cardiac circulation should be instituted. There is no specific antidote. An evacuation of the stomach is recommended by emetics and gastric lavage after which the electrolyte and fluid balance should be evaluated carefully.

DOE AND ADMINISTRATION
Hypertension: The adult starting indapamide dose is 1.25 mg as a single daily dose taken in the morning. If the response is 1.25 mg is not satisfactory after four weeks, the daily dose may be increased to 2.5 mg taken once daily. If the response to 2.5 mg is not satisfactory after four weeks, the daily dose may be increased to 5.0 mg taken once daily, but adding another antihypertensive should be considered.
Edema of congestive heart failure: The adult starting indapamide dose for edema of congestive heart failure is 2.5 mg as a single daily dose taken in the morning. If the response to 2.5 mg is not satisfactory after one week, the dose may be increased to 5.0 mg taken once daily.
If the antihypertensive response to indapamide is insufficient, indapamide may be combined with other antihypertensive drugs, with careful monitoring of blood pressure. It is recommended that the usual dose of other agents be reduced by 50% during initial combination therapy. As the blood pressure response becomes evident, further dosage adjustments may be necessary.
In general, doses of 5 mg and larger have not appeared to provide additional effects on blood pressure or heart failure, but are associated with a greater degree of hypokalemia. There is minimal clinical trial experience in patients with doses greater than 5.0 mg once daily.

HOW SUPPLIED
Indapamide Tablets are available as follows:
1.25 mg (Orange film coated, normal convex, round tablet, debossed '1' on one side and '87' on the reverse)
Bottles of 100 NDC 57315-027-01
Bottles of 1000 NDC 57315-027-02

2.5 mg (White film coated, normal convex, round tablet, debossed '1' on one side and 'G' on the reverse)
Bottles of 100 NDC 57315-028-01
Bottles of 1000 NDC 57315-028-02

CAUTION:
Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at controlled room temperature,
10°-30°C (50°-86°F).
Avoid excessive heat. Dispense in light resistant containers as defined in USP.
Manufactured by: ALPHAPHARMA PTY., LTD.
Cnr. Garnet & Alinyms Sts.,
Carole Park, Qld. 4300
Australia
Call 1-800-661-3429 Revised November 1997

484/0

TABLE 2: Adverse Reactions from Studies of 2.5 mg and 5.0 mg
Incidence ≥ 5%  Incidence ≥ 5%
DERMATOLOGIC
Rash  Hives
Allergy  Pruritus
Hypersensitivity
Impotence or reduced sex drive  Rhinorrhea
Pustular  flushing  Hyperuricemia
Blood  Hyperglycemia  Hyperkalemia
Type 2 diabetes  Hypochromia  Increased serum uric acid
Serum creatinine
Glycosuria  Weight loss
Dry mouth  Tingling of extremities

Because most of these data are from long-term studies (up to 40 weeks of treatment), it is probable that many of these experiences were due to causes other than the drug. Approximately 10% of patients given indapamide discontinued treatment in long-term trials because of reactions either related or unrelated to the drug.
Hypokalemia with concurrent clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemia effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients tolerating indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. In the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention.
In clinical trials of six to eight weeks, the mean changes in selected values were as shown in the table below.

Mean Changes from Baseline after 6 Weeks of Treatment: 1.25 mg

<table>
<thead>
<tr>
<th>Function</th>
<th>Indapamide (1.25 mg)</th>
<th>Hydrochlorothiazide (5 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Electrolyte</td>
<td>(mEq/L)</td>
<td>(mEq/L)</td>
</tr>
<tr>
<td>Sodium</td>
<td>139 ± 3</td>
<td>141 ± 3</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5 ± 0.35</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>Chloride</td>
<td>99 ± 4</td>
<td>103 ± 6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Urea</td>
<td>53 ± 20</td>
<td>46 ± 20</td>
</tr>
</tbody>
</table>

BUN
<table>
<thead>
<tr>
<th>Function</th>
<th>Indapamide (1.25 mg)</th>
<th>Hydrochlorothiazide (5 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Electrolyte</td>
<td>(mEq/L)</td>
<td>(mEq/L)</td>
</tr>
<tr>
<td>Sodium</td>
<td>139 ± 3</td>
<td>141 ± 3</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5 ± 0.35</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>Chloride</td>
<td>99 ± 4</td>
<td>103 ± 6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Urea</td>
<td>53 ± 20</td>
<td>46 ± 20</td>
</tr>
</tbody>
</table>

Indapamide had no adverse effects on lipids.

The following reactions have been reported with clinical usage of indapamide: jaundice (intrarenal cholestatic jaundice), hepatitis, and abnormal liver function tests. These reactions were reversible with discontinuance of the drug. Also reported are erythema multiforme, Stevens-Johnson Syndrome, febrile reactions, purpura, photosensitivity, fever, pneumonia, anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia and aplastic anemia. Other adverse reactions reported with antihypertensive drugs are necrotizing angiitis, respiratory distress, salaradens, xanthoplasia.

The following reactions have been reported with clinical usage of indapamide: jaundice (intrarenal cholestatic jaundice), hepatitis, and abnormal liver function tests. These reactions were reversible with discontinuance of the drug. Also reported are erythema multiforme, Stevens-Johnson Syndrome, febrile reactions, purpura, photosensitivity, fever, pneumonia, anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia and aplastic anemia. Other adverse reactions reported with antihypertensive drugs are necrotizing angiitis, respiratory distress, salaradens, xanthoplasia.
See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Avoid excessive heat.

Dispense in tight containers as defined in USP.

Each tablet contains:

Indapamide 2.5 mg

INDAPAMIDE TABLETS USP
2.5 mg
100 tablets

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Alphapharm

Lot No.: 4400

Exp. Date: 4/2020

Manufactured by ALPHAPHARM PTY LTD.
Cnr. Carled & Autumn Sts.,
Canley Park, Qld. 4300
Australia
Call 1-800-9913429

NDC 57315-028-01

INDAPAMIDE TABLETS USP
2.5 mg
1000 tablets

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Alphapharm

Lot No.: 4400

Exp. Date: 4/2020

Manufactured by ALPHAPHARM PTY LTD.
Cnr. Carled & Autumn Sts.,
Canley Park, Qld. 4300
Australia
Call 1-800-9913429

NDC 57315-028-02
QUARANTINE HOLD

INDAPAMIDE TABLETS USP, 2.5 mg
NDC 57315-028-03

LOT NO.: BULK EXP.DATE:
GROSS WT.: TARE WT.:
NET WT.: ATW:
NO. OF TABLETS: DATE OF MANUFACTURE:

SIGNED BY: _________________ DATE: ______

Each tablet contains Indapamide USP 2.5 mg

Store at controlled room temperature, 15° to 30° C (59° to 86° F).

ALPHAPHARM PTY. LTD.

BRISBANE, AUSTRALIA

1 - 800 - 661 3429

CAUTION: Federal law prohibits dispensing without prescription.
For further manufacturing, processing or repacking.
ALPHAPHARM PTY LTD
APPROVED FOR REPACKING
INDAPAMIDE TABLETS USP 1.25 MG
LOT NUMBER
APPROVED BY
03 - Dec - 97

ALPHAPHARM PTY LTD
APPROVED FOR REPACKING
INDAPAMIDE TABLETS USP 1.25 MG
LOT NUMBER
APPROVED BY
03 - Dec - 97

ALPHAPHARM PTY LTD
APPROVED FOR REPACKING
INDAPAMIDE TABLETS USP 1.25 MG
LOT NUMBER
APPROVED BY
03 - Dec - 97