

NEW ZEALAND DATA SHEET

DAPA-TABS

Indapamide hemihydrate Tablet 2.5 mg



Presentation

DAPA-TABS 2.5 mg Tablets: 6.5mm, normal convex, pink, film coated tablet debossed "IE" over "2.5" on one side and "G" on the other. Each DAPA-TABS tablet contains 2.5 mg of indapamide hemihydrate.

Do not halve DAPA-TABS tablets.

Uses

Actions

Indapamide is an oral antihypertensive agent. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions may be involved.

At a dose of 2.5 mg, the renal effects of indapamide are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity to functionally anephric patients lends support to the hypothesis.

The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 2.5 mg/day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalaemia (plasma potassium <3.2 mmol/L) has been reported in some 10% of patients.

Indapamide hemihydrate 2.5 mg daily does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

Pharmacokinetics

Possibly due to its high lipid solubility, absorption of indapamide from the gastrointestinal tract is rapid (within 0.5 to 1 hour after an oral dose) and complete. Bioavailability of the tablet formulation is 100% and is virtually unchanged with food or antacids.

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80%) and, more specifically, to carbonic acid anhydrase (98%) without significantly inhibiting this enzyme. In plasma, it is relatively highly bound to plasma proteins (79%). It is also taken up to a significant degree in the vascular compartment, the drug has a relatively low apparent volume of distribution (approximately 60 L) and 40% of the dose is located in the blood one hour after administration.

After a single dose of 2.5 mg, as well as after repeated administration of 2.5 mg daily for 15 days, plasma elimination half-life of unchanged indapamide is biphasic with half lives of 14 to 25 hours, indicating that once daily dosing is possible and that no change in kinetics occurs after repeated dosing. Both single and multiple dose data indicate that indapamide's kinetics are linear. Steady-state plasma levels are reached within three to four days after starting treatment and the drug does not accumulate in hypertensive patients with various degrees of renal insufficiency.

Indapamide is extensively metabolised in the liver. Following radioactivity studies using carbon-14, the main route of elimination is the urine, but only 5 to 7% of the dose is excreted into the urine as unchanged drug;

20 to 23% of total radioactivity is eliminated into the faeces. Renal clearance of indapamide (as unchanged drug) is approximately 5 mL/minute, representing less than 10% of systemic clearance.

The high lipid solubility of the indoline moiety confers to indapamide its highly localised binding to structures in the cardiovascular system.

Indications

Essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally indapamide is used as the initial agent in multiple drug regimens.

Dosage and Administration

One tablet of DAPA-TABS (2.5 mg indapamide) daily to be taken in the morning. The action of DAPA-TABS is progressive and whilst the optimum reduction in blood pressure is usually seen after four weeks, a further small but useful reduction in blood pressure may be observed over the following four to six weeks. A larger dose than 1 tablet (2.5 mg) of DAPA-TABS daily is not recommended as there is little additional antihypertensive effect, whilst the diuretic effect becomes more prominent.

A single daily tablet of DAPA-TABS may effectively be combined with the following antihypertensive agents: beta-blockers, methyldopa, clonidine, prazosin, and ACE inhibitors.

Combination with a diuretic agent is not recommended as significant electrolyte disturbances may ensue. Indapamide has a slight but significant carry-over hypotensive effect lasting up to 1 or 2 weeks after the cessation of therapy.

Do not halve DAPA-TABS tablets.

Contraindications

Anuria, progressive and severe oliguria, hepatic coma. Known hypersensitivity to DAPA-TABS or to other sulfonamide derivatives.

Warnings and Precautions

Electrolyte imbalance. Patients receiving DAPA-TABS should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemia and hypokalaemia. Blood urea, nitrogen and uric acid should also be assessed during therapy.

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.

Electrolyte changes. Electrolyte changes observed with indapamide become more prominent at doses above 2.5 mg/day. The daily maximum recommended dose of DAPA-TABS is 2.5 mg administered as one tablet, since doses above 2.5 mg only increase the diuretic effect and electrolyte disturbances consequent to diuresis without any further appreciable antihypertensive effect.

Hypokalaemia. Hypokalaemia may occur at all doses. (Symptoms of hypokalaemia include weakness, cramps, and cardiac dysrhythmias. Hypokalaemia is a particular hazard in digitalised patients; dangerous or fatal arrhythmias may be precipitated.)

Hypokalaemia will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake.

Although indapamide 2.5 mg daily can be safely administered to hypertensive patients with impaired renal function, caution should be observed when the drug is administered to patients with severe renal impairment since the unchanged drug is excreted primarily by the renal route.

Hyperuricaemia. Hyperuricaemia may occur during administration of indapamide. Gout has rarely been reported.

Impaired Renal Function. Although DAPA-TABS 2.5 mg daily, can safely be administered to hypertensive patients with impaired renal function, the treatment should be discontinued if increasing azotaemia and oliguria occur. Studies in functionally anephric patients for one month undergoing chronic haemodialysis have not shown evidence of drug accumulation, despite the fact that indapamide is not dialysable.

Lithium. In general, diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity.

Severe Hepatic Disease. Special caution should be used in treating patients with severe hepatic disease to avoid metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

Hypotension. 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.

Skin Reactions. Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also been reported to be associated with sulfonamides. These possibilities should be kept in mind with the use of DAPA-TABS.

Use in Pregnancy:

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose.

There is no information on the use of indapamide in pregnancy. Whilst animal studies have not suggested any teratogenic effect, DAPA-TABS is not recommended for administration to pregnant women unless the expected benefit outweighs the potential risk.

Use in Lactation:

It is not known whether indapamide is excreted in breast milk. It is therefore not recommended that the drug be given to lactating women as the possible effect on the newborn is unknown.

Paediatric Use:

Safety and effectiveness have not been established.

Adverse Effects

In general, most adverse effects are mild and transient with the most frequently reported being asthenia, dizziness, headache, fatigue, muscle cramps and gastrointestinal disturbances, usually occurring within the first month of treatment. Other adverse reactions have been non-specific. Cutaneous rash and impotence have been occasionally reported. Percentages shown below indicate the incidence in clinical trials.

The most severe and common adverse effect is electrolyte imbalance.

Electrolyte changes reported include: hypokalaemia: serum potassium < 3.4 mmol/L – up to 25%, serum potassium < 3.2 mmol/L - up to 10% (potassium supplementation may be required in up to 25% of cases); hypochloraemia - 9.4%; hyponatraemia - 3.1%.

Central Nervous System (8.1%).

Incidence > 1% < 3%: asthenia, headache, dizziness, vertigo.

Incidence < 1%: drowsiness, sleepiness, insomnia, weakness, lethargy, visual disturbance.

Gastrointestinal (2.6%).

Incidence < 1%: nausea/anorexia, dryness of mouth, gastralgia, vomiting, diarrhoea, constipation.

Musculoskeletal (1.4%).

Incidence > 1% < 3%: muscle cramps.

Incidence < 1%: joint pain, back pain, weakness of legs.

Cardiovascular (1%).

Incidence < 1%: orthostatic hypotension, tachycardia, ECG changes (non specific ST-T changes, U waves, left ventricular strain).

Urogenital (0.5%).

Incidence < 1%: impotence, modification of libido, polyuria.

Dermatological (0.5%).

Incidence < 1%: rash, pruritus.

Endocrine (0.2%).

Incidence < 1%: gout.

Other (0.5%).

Incidence < 1%: tinnitus, malaise/fainting, sweat.

Laboratory Abnormalities.

The following values represent the maximum variations from pre-treatment values in occasional patients at some stage during, but not necessarily throughout, treatment. Blood uric acid up 8.6%, blood glucose up 6%, BUN up 5.7%, blood creatinine up 3.6%.

Interactions

No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants, uricosurics and anti-inflammatory agents.

It is recommended that the drug not be used in combination with a diuretic agent since the combination may produce hypokalaemia and hyperuricaemia.

Overdosage

Symptoms. There have been no reports of overdosage. Based on the pharmacological activities of 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.

Pharmaceutical Precautions

Store below 30°C.

Medicine Classification

Prescription Medicine.

Package Quantities

2.5 mg tablets: Blister packs of 30 and 90 tablets.

Not all pack sizes may be marketed.

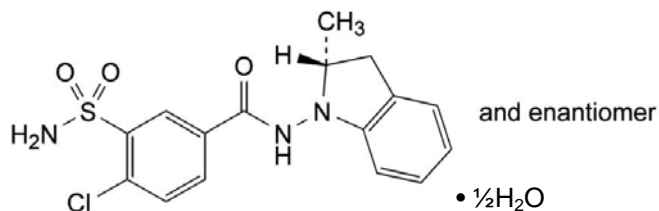
Further Information

Name of the medicine

Active ingredient: Indapamide hemihydrate

Chemical name: 4-chloro-*N*-[(2*RS*)-2-methyl-2,3-dihydro-1*H*-indol-1-yl]-3-sulphamoylbenzamide hemihydrate

Structural formula:



Molecular formula: $\text{C}_{16}\text{H}_{16}\text{ClN}_3\text{O}_3\text{S}, \frac{1}{2}\text{H}_2\text{O}$

Molecular weight: 374.85

CAS Registry No.: 26807-65-8

Description

Indapamide is a nonthiazide indole derivative of chlorosulfonamide.

Indapamide is a 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. Melting point is approximately 185°C.

Each DAPA-TABS tablet contains 2.5 mg indapamide hemihydrate as the active ingredient. The tablets also contain the following inactive ingredients: sodium starch glycollate, magnesium stearate, cellulose – microcrystalline, lactose anhydrous, croscarmellose sodium, Opadry Pink OY-6953.

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Date of Preparation

4 May 2010

