For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

DITIDE

Triamterene and Benzthiazide Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Benzthiazide 25 mg
Triamterene IP 50 mg
Colour : Indigo Carmine.

PHARMACEUTICAL FORM

Uncoated tablet.

CLINICAL PARTICULARS

Therapeutic Indications

For the control of oedema in cardiac failure, cirrhosis of the liver or nephrotic syndrome, and in that associated with corticosteroid treatment.

Posology and Method of Administration

Method of Administration

For oral use.

Posology

Adults Only

The optimal dosage is three tablets a day, two being taken after breakfast and one after lunch. After the first week, treatment should preferably be given on alternative days, to ensure satisfactory maintenance diuresis without an increase in blood urea levels. Maintenance dosage may be reduced to one or two tablets every other day, taken after breakfast or after breakfast and lunch. When given with another diuretic, lower dosages of both should be used initially.

Elderly

A lower dosage may be sufficient. The normally occurring reduction in glomerular filtration with age must be borne in mind.

Contraindications

DITIDE is contraindicated in:
• Hyperkalaemia
• Progressive renal failure
• Increasing hepatic dysfunction
• Hypercalcaemia
• Diabetic ketoacidosis
• Anuria
• Addison’s disease
• Known hypersensitivity to either constituent of the product
• Routine concomitant administration of potassium supplements, or other potassium-conserving drugs, including Angiotensin Converting Enzyme (ACE) inhibitors
• Pregnancy (see Pregnancy and Lactation)
• Breast-feeding (see Pregnancy and Lactation).

Special Warnings and Special Precautions for Use

Use with caution in patients with diabetes mellitus, hepatic or renal insufficiency; in those predisposed to gout, since both components can elevate uric acid levels; with hypotensive agents since an additive effect may result; in diabetic patients since thiazides can provoke hyperglycaemia and glycosuria; in diabetic nephropathy due to increased risk of hyperkalaemia.

It is advisable to monitor blood urea, serum potassium levels and electrolytes periodically. This is important in the elderly, those with renal impairment and those receiving concomitant treatment with Nonsteroidal Anti-Inflammatory Drugs (NSAID’s).

Triamterene and thiazides reduce excretion of lithium and may thus precipitate intoxication.

Very rare cases of SLE have been reported associated with triamterene and hydrochlorothiazide.

Aggravation of pancreatitis may also occur.

Combinations of folate antagonists and triamterene are not advisable in pregnancy or in patients with hepatic cirrhosis because of the increased theoretical risk of folate deficiency developing.

*DITIDE* tablets may cause the urine to be coloured fluorescent blue.

Photosensitivity has been reported quite frequently with treatments containing triamterene. Patients must be advised about this side effect and to take adequate precautions.

**Interaction with Other Medicaments and Other Forms of Interaction**

Use with caution with hypotensive agents. When given with another diuretic, lower dosage of both should be given initially. Triamterene reduces excretion of Lithium and may thus precipitate intoxication.

It is advisable to monitor blood urea and serum potassium levels periodically in patients receiving concomitant treatment with NSAIDs. Renal failure, reversible on stopping treatment,
has been reported very rarely which may be due to an interaction between triamterene and some NSAIDs.

It has been suggested that the suppression of urinary prostaglandins by NSAIDs could potentiate the nephrotoxic effects of triamterene.

Occasional reports of reduced renal function when triamterene given with indometacin avoid concomitant use.

Interactions with other drugs have to be considered:

- Tubocurarine - increased response to this relaxant.
- Colestyramine/Colestipol - absorption of DITIDE reduced
- Insulin - DITIDE antagonizes the hypoglycaemic effect of insulin.
- Combined oral contraceptives - DITIDE effect is reduced.

Increased hypotensive effect of DITIDE by:

- Dipyridamole
- Alprostadil
- Moxisylyte
- Tizanidine
- Beta blocker eye drops
- MAOI’s

Increased postural hypotensive effect of DITIDE by:

- First dose of alpha blocker
- Alpha blockers
- Alprostadil
- ACE inhibitors
- drospirenone (monitor serum potassium during first cycle)
- adrenergic neurone blockers
- alcohol
- aldesleukin
- general anaesthetics
- angiotensin-II receptor antagonists
- Anxiolytics and hypnotics
- With baclofen
- Beta-blockers
- Calcium-channel blockers
- Clonidine
- Hydralazine
- Levodopa
- MAOIs
- Methyldopa
- Minoxidil
- Diazoxide
- Moxisylyte
• Moxonidine
• Nitrates
• Phenothiazines
• Sodium nitroprusside
• Tizanidine

Increased risk of hypercalcaemia by:
• Parenteral calcium
• Oral calcium salts

Increased risk of hyperkalaemia by:
• ACE inhibitors
• ACE inhibitors with thiazides
• Angiotensin inhibitors
• Ciclosporin
• Potassium salts
• Tacrolimus
• Trilostane
• Indomethacin
• Aliskiren
• Chlorpropamide
• Amiloride
• Aldosterone antagonists such as eplerenone and spironolactone

Increased risk of hypersensitivity with:
• Allopurinol

Increased risk of hyponatraemia with:
• Chlorpropamide
• Aminoglutethimide
• Carbamazepine

Increased risk of nephrotoxicity and antagonism of diuretic effect with:
• NSAID’s
• Ketorolac
• Indometacin
• Oestrogens
• Corticosteroids

Hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with following drugs:
• Sertindole
• Pimozide (avoid concomitant use)
• Platinum compounds
• Atomoxetine
• Amisulpride

Increased risk of postural hypotension with:
• Tricyclic antidepressants

Increased risk of renal failure with:
• Indomethacin

Lithium - increased risk of lithium toxicity

Drospirenone - may increase risk of hyperkalaemia

Mefuran, Repaglinide/Nateglinide, Sulphonylureas, Troglitazone – reduced hypoglycaemic effect

**Pregnancy and Lactation**

**Pregnancy**

The use of *DITIDE* is contraindicated during pregnancy *(see Contraindications).*

Animal studies have not suggested foetal abnormalities. Nevertheless, both triamterene and thiazides have been shown to pass through the placenta in humans and also to pass into breast milk. In rare instances, thrombocytopenia, pancreatitis or hypoglycaemia have been reported in new-born infants of mothers treated with thiazides. Nevertheless, drugs should be avoided in pregnancy unless essential, especially during the first trimester.

**Lactation**

The use of *DITIDE* is contraindicated during breast-feeding *(see Contraindications)* and if the drug is essential, the patient should stop breastfeeding.

**Effects on Ability to Drive and Use Machines**

None known.

**Undesirable Effects**

Nausea, vomiting, diarrhoea, muscle cramps, weakness, dizziness, headache, dry mouth, thirst, decreases in blood pressure hyperkalaemia, hyperuricaemia, hypovolaemia, transient renal insufficiency, serum sickness, urinary stones and rash have all been reported.

Photosensitivity and pseudoporphyria is very rare.
Weakness, minor decreases in blood pressure, and rash have been reported. Anaphylaxis is a remote possibility.
Minor serum electrolyte changes have been observed infrequently, and marked fluctuations in serum potassium levels are uncommon.

Metabolic acidosis occasionally occurs.

Hyperglycaemia, increased uric acid levels which sometimes lead to gout, and hypercalcaemia that does not lead to tertiary hyperparathyroidism may also occur.

Electrolyte imbalance may also indicate excessive dosage or be secondary to the condition under treatment.

In common with most diuretics, DITIDE may reduce glomerular filtration rate and cause a temporary increase in blood urea and creatinine levels; again this may also indicate excessive dosage or be secondary to the condition under treatment.

It can also cause increases in plasma lipid levels.

Renal failure, reversible on stopping treatment, has been reported very rarely and has been due to acute interstitial nephritis or an interaction between triamterene and some NSAID’s.

Triamterene has been found in renal stones both alone and in association with other usual calculus components. There is no evidence that stone formation is increased in patients taking triamterene containing drugs.

Triamterene interferes with bioassay of folic acid.

Rare cases of thrombocytopenic purpura, pancytopenia and megaloblastic anaemia have been reported with triamterene; thiazides alone have caused jaundice and acute pancreatitis and, rarely blood dyscrasias including agranulocytosis, thrombocytopenia and leucopenia.

Very rare cases of Abnormalities of Serum Level of Liver Enzyme have been reported associated with combined triamterene and hydrochlorothiazide.

**Overdose**

**Symptoms and signs**

Symptoms of electrolyte imbalance, especially hyperkalaemia, are likely. Symptoms include nausea, vomiting, weakness, lassitude, muscular weakness, hypotension and cardiac arrhythmias.

**Treatment**

Treatment consists of gastric lavage with careful monitoring of electrolytes and fluid balance. Cardiac rhythm should be monitored and appropriate measures taken to correct hyperkalaemia as necessary. There is no specific antidote. There may be some benefit to renal dialysis in cases of severe overdosage.

**PHARMACOLOGICAL PROPERTIES**
Pharmacodynamic Properties

Mechanism of Action and Pharmacodynamic Effects

Triamterene is a potassium conserving diuretic thought to act by directly inhibiting the exchange of sodium for potassium and hydrogen in the distal renal tubule.

Benzthiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excreting of sodium and chloride ions, and consequently of water. Potassium ions are excreted to a lesser extent.

Pharmacokinetic Properties

Onset of diuresis takes place within one hour, peaks at 2-3 hours and tapers off during the subsequent 7-9 hours.

Triamterene is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It has been estimated to have a plasma half-life of about 2 hours. It is extensively metabolised and is mainly excreted in the form of metabolites with some unchanged triamterene; variable amounts are also excreted in the bile.

Benzthiazide is poorly absorbed from the gastro-intestinal tract, and is excreted almost entirely unchanged in the urine.

Preclinical Safety Data

There are no relevant data available.

PHARMACEUTICAL PARTICULARS

List of Excipients

Starch, Lactose, Polyvinyl Pyrrolidone K-30, Isopropyl alcohol, Sodium lauryl sulphate, Indigo carmine, Sodium starch glycollate, Magnesium stearate.

Incompatibilities

No data available

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store in a dry place at temperatures not exceeding 30°C.

Keep out of reach of children.
Nature and Specification of Container

Blister strips (Aluminium/PVC) in a carton

Instructions for Use / Handling

There are no special requirements for use or handling of the product.

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Adapted from:
- SmPC for Triamterene on eMC website, date of revision of text 05 Sep 2014
- Benzthiazide Martindale website, date of revision of text 10-May-2018