

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Moduret 25 mg/2.5 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg hydrochlorothiazide and amiloride hydrochloride equivalent to 2.5 mg anhydrous amiloride hydrochloride.

Excipients: Each tablet contains 35.5 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Off-white, diamond-shaped tablets, with a break-line and marked with identification number '923'. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Potassium-conserving diuretic and antihypertensive.

Moduret 25 mg/2.5 mg is indicated alone or as an adjunct to other antihypertensive agents in the treatment of hypertension.

Moduret 25 mg/2.5 mg is intended for the treatment of patients in whom potassium depletion might be suspected or anticipated. The presence of amiloride hydrochloride reduces the likelihood of potassium loss during diuresis for long term maintenance therapy. The combination is thus indicated especially in conditions where potassium balance is particularly important.

4.2 Posology and method of administration

The usual dose is one 'Moduret 25 mg/2.5 mg' tablet once a day. In some patients, a starting dose of half a tablet once a day may be sufficient.

Paediatric use:

Moduret 25 mg/2.5 mg is not recommended for children. (*See 4.3 'Contra-indications'*).

Use in elderly:

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance; the dosage should be carefully adjusted to renal function and clinical response.

See 4.4 'Special Warnings and Special Precautions for Use, Electrolyte imbalance.'

4.3 Contraindications

Hyperkalaemia (plasma potassium over 5.5 mmol/l); other potassium-conserving diuretics. Potassium supplements or potassium-rich food (except in severe and/or refractory cases of hypokalaemia under careful monitoring); anuria; acute renal failure, severe progressive renal disease, severe hepatic failure, precoma associated with hepatic cirrhosis, Addison's disease, hypercalcaemia, concurrent lithium therapy, diabetic nephropathy; patients with blood urea over 10 mmol/l, patients with diabetes mellitus, or those with serum creatinine over 130 µmol/l in whom serum electrolyte and blood urea levels cannot be monitored carefully and frequently. Prior hypersensitivity to amiloride hydrochloride, hydrochlorothiazide or other sulphonamide derived drugs. Because the safety of amiloride hydrochloride for use in children has not been established, Moduret 25 mg/ 2.5 mg is not recommended for children. For '*Use in pregnancy*' and '*Use in breast-feeding mothers*'; see 4.6 '*Pregnancy and Lactation*.'

4.4 Special warnings and precautions for use

Hyperkalaemia has been observed in patients receiving amiloride hydrochloride, either alone or with other diuretics, particularly in the aged or in hospital patients with hepatic cirrhosis or congestive heart failure with renal involvement, who were seriously ill, or were undergoing vigorous diuretic therapy. Such patients should be carefully observed for clinical, laboratory, and ECG evidence of hyperkalaemia (not always associated with an abnormal ECG).

Neither potassium supplements nor a potassium-rich diet should be used with Moduret 25 except under careful monitoring in severe and/or refractory cases of hypokalaemia.

Some deaths have been reported in this group of patients.

Treatment of hyperkalaemia: Should hyperkalaemia develop, discontinue treatment immediately and, if necessary, take active measures to reduce the plasma potassium to normal.

Impaired renal function: Renal function should be monitored because the use of Moduret 25 in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine clearance falls below 30 ml/min.

Electrolyte imbalance: Although the likelihood of electrolyte imbalance is reduced by Moduret 25, careful check should be kept for such signs of fluid and electrolyte imbalance as hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia.

It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid or electrolyte imbalance include: dryness of the mouth, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea and vomiting.

Hypokalaemia may develop, especially as a result of brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Diuretic-induced hyponatraemia is usually mild and asymptomatic. It may become severe and symptomatic in a few patients who will then require immediate attention and appropriate treatment.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Therapy should be discontinued before carrying out tests for parathyroid function.

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance.

Uraemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing uraemia and oliguria develop during treatment of renal disease, Moduret 25 should be discontinued.

Hepatic disease: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease (*see 4.3 'Contra-indications'*), since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic: Hyperuricaemia may occur, or gout may be precipitated or aggravated, in certain patients receiving thiazides. Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by therapy with Moduret 25 (*see 4.3 'Contra-indications'*). Dosage adjustment of antidiabetic agents, including insulin, may be required.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

To minimise the risk of hyperkalaemia in diabetic or suspected diabetic patients, the status of renal function should be determined before initiating therapy with Moduret 25. Therapy should be discontinued at least three days before giving a glucose tolerance test. Potassium-conserving therapy should be initiated only with caution in severely ill patients in whom metabolic or respiratory acidosis may occur, e.g. patients with cardiopulmonary disease or patients with inadequately controlled diabetes.

Shifts in acid-base balance alter the balance of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in plasma potassium.

Sensitivity reactions: The possibility that thiazides may activate or exacerbate systemic lupus erythematosus has been reported.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations.

Non-Steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors:

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of antihypertensive drugs, including the diuretic, natriuretic and antihypertensive effects of diuretics.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Concomitant administration of NSAIDs and potassium-sparing agents, including amiloride HCl, may cause hyperkalemia, particularly in elderly patients. Therefore when amiloride HCl is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored.

Amiloride Hydrochloride

When amiloride hydrochloride is administered concomitantly with an ACE inhibitor, an angiotensin II receptor antagonist, cyclosporin or tacrolimus, the risk of hyperkalaemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics: Co-administration may potentiate orthostatic hypotension.

Oral and parenteral antidiabetic drugs may require adjustment of dosage with concurrent use. Moduret 25 mg/2.5 mg can act synergistically with chlorpropamide to increase the risk of hyponatraemia. **Other antihypertensive drugs** may have an additive effect. Therefore the dosage of these agents, especially adrenergic-blockers, may need to be reduced when Moduret 25 mg/ 2.5 mg is added to the regimen. Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with an ACE inhibitor to reduce the likelihood of first dose hypotension. **Cholestyramine and colestipol resins:** absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids or ACTH may intensify any thiazide-induced electrolyte depletion, particularly hypokalaemia. **Pressor-amines such as epinephrine (adrenaline)** may show decreased arterial responsiveness when used with Moduret 25 mg/2.5 mg but this reaction is not enough to preclude their therapeutic usefulness. **Non-depolarising muscle relaxants such as tubocurarine** may possibly interact with Moduret 25 mg/2.5 mg to increase muscle relaxation. **Drug/laboratory tests:** Because thiazides may affect calcium metabolism, Moduret 25 mg/2.5 mg may interfere with tests for parathyroid function.

4.6 Fertility, pregnancy and lactation

Use in pregnancy: The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated, because they may be associated with hypovolaemia, increased blood viscosity, and decreased placental perfusion. Diuretics do not prevent the development of toxemia of pregnancy and there is no satisfactory evidence that they are useful for its treatment.

Since thiazides cross the placental barrier and appear in cord blood, use where pregnancy is present or suspected requires that the benefits of the drug be weighed against possible hazards to the foetus. These hazards include foetal or neonatal jaundice, thrombocytopenia, bone marrow depression and possibly other side effects that have occurred in the adult.

Use in breast-feeding mothers: Although it is not known whether amiloride hydrochloride is excreted in human milk, it is known that thiazides do appear in breast milk. If use of the drug combination is deemed essential, the patient should stop breast-feeding.

4.7 Effects on ability to drive and use machines

Infrequently, patients may experience weakness, fatigue, dizziness, stupor and vertigo. Should any of these occur, the patient should be cautioned not to drive or operate machinery.

4.8 Undesirable effects

Although minor side effects are relatively common, significant side effects are infrequent.

Reported side effects are generally associated with diuresis, thiazide therapy, or with the underlying disease.

No increase in the risk of adverse reactions has been seen over those of the individual components.

The following side effects have been reported with MODURET 25mg /2.5mg Tablets:

Immune system disorders:

Anaphylactic reaction

Metabolism and nutrition disorders:

elevated plasma potassium levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia (*See 4.4 'Special warnings and precautions for use'*), gout, dehydration, symptomatic hyponatraemia.

Psychiatric disorders:

Diaphoresis, insomnia, nervousness, mental confusion, depression, sleepiness.

Nervous system disorder:

Headache, dizziness, vertigo, paraesthesiae, stupor

Eye disorders:

visual disturbance

Cardiac disorders:

arrhythmias, tachycardia, digitalis toxicity, angina pectoris.

Vascular disorders:

orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Dyspnoea, nasal congestion.

Gastrointestinal disorders:

bad taste, anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain, GI bleeding, appetite changes, abdominal fullness, flatulence, thirst, hiccups.

Skin and subcutaneous tissue disorders:

Flushing, rash, pruritis

Musculoskeletal, connective tissue and bone disorders:

back pain, leg ache, muscle cramps, joint pain

Renal and urinary disorders:

impotence, dysuria, nocturia, incontinence, renal dysfunction including renal failure.

General disorders and administration site conditions:

weakness, fatigue, malaise, chest pain, syncope

Additional side effects that have been reported with the individual components and may be potential side effects of MODURET 25mg /2.5mg Tablets are listed below:

Amiloride:

Psychiatric disorders:

decreased libido, somnolence

Nervous system disorder:

tremors, encephalopathy

Eye disorders:

increased intra-ocular pressure

Ear and labyrinth disorders:

tinnitus

Cardiac disorders:

one patient with partial heart block developed complete heart block, palpitation

Blood and lymphatic system disorders:

aplastic anaemia, neutropenia

Respiratory, thoracic and mediastinal disorders:

Cough

Gastrointestinal disorders:

Dry mouth, activation of probable pre-existing peptic ulcer, dyspepsia

Hepatobiliary disorders:

abnormal liver function, jaundice

Musculoskeletal, connective tissue and bone disorders:

neck/shoulder ache, pain in extremities

Renal and urinary disorders:

polyuria, urinary frequency, bladder spasm

General disorders and administration site conditions:

Alopecia

Hydrochlorothiazide:

Endocrine disorders:

glycosuria, hyperglycaemia, hyperuricaemia, hypokalaemia.

Vascular disorders:

necrotising angitis (vasculitis, cutaneous vasculitis).

Gastrointestinal disorders:

pancreatitis, cramping, gastric irritation.

Hepatobiliary disorders:

Jaundice (intrahepatic cholestatic jaundice)

General disorders and administration site conditions:

fever

Skin and subcutaneous tissue disorders:

urticaria, toxic epidermal necrolysis

Blood and lymphatic system disorders:

agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, purpura, thrombocytopenia.

Psychiatric disorders:

restlessness.

Renal and urinary disorders:

interstitial nephritis.

Respiratory, thoracic and mediastinal disorders:

respiratory distress, including pneumonitis, pulmonary oedema.

Eye disorders:

transient blurred vision, xanthopsia.

General disorders and administration site conditions:

photosensitivity, sialadenitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No specific data are available on overdosage with Moduret 25. No specific antidote is available, and it is not known whether the drug is dialysable.

Treatment should be symptomatic and supportive. Therapy should be discontinued and the patient watched closely. Emesis should be induced and/or gastric lavage performed. The most common signs and symptoms of overdosage with amiloride hydrochloride are dehydration and electrolyte imbalance. Blood pressure should be monitored and corrected where necessary. If hyperkalaemia occurs, active measures should be taken to reduce the plasma potassium levels.

Electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration are the most common signs and symptoms of hydrochlorothiazide overdosage. If digitalis has been administered, hypokalaemia may accentuate cardiac arrhythmias.

The plasma half-life of hydrochlorothiazide is 5.6 hours with a subsequent longer terminal half-life; the plasma half-life of amiloride is about six hours.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC Code: C03EA01 – Hydrochlorothiazide and potassium – sparing agents

Moduret 25 provides diuretic and antihypertensive activity (principally due to the hydrochlorothiazide component), while acting through the amiloride components to prevent excessive potassium loss that may occur in patients receiving a thiazide diuretic. Due to this latter component, the urinary excretion of magnesium is less with Moduret 25 than with a thiazide or loop diuretic used alone. The onset of the diuretic action of Moduret 25 is within 1 to 2 hours and this action appears to be sustained for approximately 24 hours.

5.2 Pharmacokinetic properties

Amiloride hydrochloride usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride hydrochloride up to approximately 15 mg.

Amiloride hydrochloride is not metabolised by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of amiloride hydrochloride is excreted in the urine and 40 percent in the stool within 72 hours. Amiloride hydrochloride has little effect on glomerular filtration rate or renal blood flow. Because amiloride hydrochloride is not metabolised by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

The onset of the diuretic action of hydrochlorothiazide occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

The mechanism of the antihypertensive effect of thiazides may be related to the excretion and redistribution of body sodium. Hydrochlorothiazide usually does not cause clinically important changes in normal blood pressure.

5.3 Preclinical safety data

No further information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate (E 341)

Guar galactomannan

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Pregelatinised maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

PVC/A1-PVC blister pack of 28 tablets, showing days of the week.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited

Red Oak North

South County Business Park

Leopardstown

Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1286/14/1

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