SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Milorex 5 mg/50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amiloride hydrochloride dihydrate equivalent to 5 mg anhydrous amiloride hydrochloride and 50 mg hydrochlorothiazide.

Excipients with known effect
Each tablet contains 104.1 mg lactose and 0.3 mg Sunset Yellow E110 FCF.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Peach, diamond-shaped tablets, embossed with Remedica's logo on one side and scored and embossed with 5/50 and MLX on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Potassium-conserving diuretic and antihypertensive.

Milorex is indicated in patients with: hypertension, congestive heart failure, hepatic cirrhosis with ascites and oedema. In hypertension, Milorex may be used alone or in conjunction with other antihypertensive agents.

Milorex is intended for the treatment of patients in whom potassium depletion might be suspected or anticipated. The presence of amiloride hydrochloride dihydrate minimises the likelihood of potassium loss during vigorous 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

Posology
Hypertension

Initially half a Milorex tablet given once a day. If necessary, increase to one Milorex tablet given once a day or in divided doses.

Congestive heart failure
Initially half a Milorex tablet a day, subsequently adjusted if required, but not exceeding two Milorex tablets a day. Optimal dosage is determined by the diuretic response and the plasma potassium level. Once an initial diuresis has been achieved, reduction in dosage may be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Patients with hepatic cirrhosis with ascites
Initiate therapy with a low dose. A single daily dose of one Milorex tablet may be increased gradually until there is an effective diuresis. Dosage should not exceed two Milorex tablets a day. Maintenance dosages may be lower than those required to initiate diuresis; dosage reduction should therefore be attempted when the patient's weight is stabilised. A gradual weight reduction is especially desirable in cirrhotic patients to reduce the likelihood of untoward reactions associated with diuretic therapy.

Paediatric population
Milorex is contraindicated in children under 18 years because safety and efficacy have not been established (see section 4.3).

Elderly patients
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.

Method of administration
Oral administration.

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); concomitant use with spironolactone or triamterene; 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. Because the safety of amiloride hydrochloride dihydrate for use in children has not been established, Milorex is not recommended for children under 18 years of age. For use in pregnancy and breast-feeding mothers, see section 4.6.

Hypersensitivity to the active substance(s), to any sulphonamide-derived drugs, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hyperkalaemia
Has been observed in patients receiving amiloride hydrochloride dihydrate, 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 Milorex 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 Milorex in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine levels fall below 30 ml/min.

Electrolyte imbalance
Although the likelihood of electrolyte imbalance is reduced by Milorex, 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.

Azotaemia
Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing

azotaemia and oliguria develop during treatment of renal disease, Milorex 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 Milorex (see 4.3 Contraindications). 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 Milorex. 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.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.
Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Milorex should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium
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 hydrochloride dihydrate, may cause hyperkalaemia particularly in elderly

patients. Therefore, when amiloride hydrochloride dihydrate is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored.

Amiloride hydrochloride dihydrate
When amiloride hydrochloride dihydrate is administered concomitantly with an angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, trilostane, 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 thaizide diuretics:

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

Oral and parenteral antidiabetic drugs may require adjustment of dosage with concurrent use. Milorex 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 Milorex 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. When cholestyramine is given 4 hours after the hydrochlorothiazide, the absorption of hydrochlorothiazide is reduced by 30 to 35 percent.

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 Milorex but this reaction is not enough to preclude their therapeutic usefulness.

Non-depolarising muscle relaxants such as tubocurarine may possibly interact with Milorex to increase muscle relaxation.

Drug/laboratory tests: Because thiazides may affect calcium metabolism, Milorex may interfere with tests for parathyroid function.

4.6 Fertility, pregnancy and lactation

Pregnancy
Diuretics

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 toxaemia of pregnancy and there is no satisfactory evidence that they are useful for its treatment.

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance, bone marrow depression and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding
Although it is not known whether amiloride hydrochloride dihydrate is excreted in human milk, it is known that hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Milorex during breast-feeding is not recommended. If Milorex is used during breast-feeding, doses should be kept as low as possible.

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 amiloride hydrochloride dihydrate:

Body as a whole: anaphylactic reaction, headache*, weakness*, fatigue, malaise, chest pain, back pain, syncope.

Cardiovascular: arrhythmias, tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris.

Digestive: anorexia*, nausea*, vomiting, diarrhoea, constipation, abdominal pain, GI bleeding, appetite changes, abdominal fullness, flatulence, thirst, hiccups.

Metabolic: elevated plasma potassium levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia (see section 4.4), gout, dehydration, symptomatic hyponatraemia.

Integumentary: rash*, pruritus, flushing, diaphoresis.

Musculoskeletal: leg ache, muscle cramps, joint pain.

Nervous: dizziness*, vertigo, paraesthesiae, stupor.

Psychiatric: insomnia, nervousness, mental confusion, depression, sleepiness.

Respiratory: dyspnoea.

Special senses: bad taste, visual disturbance, nasal congestion.

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

Additional side effects that have been reported with the individual components and may be potential side effects of Milorex are listed below:

Amiloride
Body as a whole: neck/shoulder ache, pain in extremities.

Digestive: abnormal liver function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice.

Integumentary: dry mouth, alopecia.

Nervous: tremors, encephalopathy.

Haematological: aplastic anaemia, neutropenia.

Cardiovascular: one patient with partial heart block developed complete heart block, palpitation.

Psychiatric: decreased libido, somnolence.

Respiratory: cough.

Special senses: tinnitus, increased intra-ocular pressure.

Urogenital: polyuria, urinary frequency, bladder spasm.

Hydrochlorothiazide
Body as a whole: fever.

Cardiovascular: necrotising angiitis (vasculitis, cutaneous vasculitis).

Digestive: jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation.

Endocrine/Metabolic: glycoscuria, hyperglycaemia, hyperuricaemia, hypokalaemia.

Integumentary: photosensitivity, sialadenitis, urticaria, toxic epidermal necrolysis.

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

Psychiatric: restlessness.

Renal: interstitial nephritis.

Respiratory: respiratory distress, including pneumonitis, pulmonary oedema, acute respiratory distress syndrome (ARDS) (see section 4.4).

Special senses: transient blurred vision, xanthopsia. Choroidal effusion (frequency not known).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

Malta
ADR Reporting Website
www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

No specific data are available on overdosage with amiloride hydrochloride dihydrate. 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 dihydrate 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics; diuretics and potassium–sparing agents in combination, ATC code: C03EA01

Mechanism of action
Hydrochlorothiazide is a diuretic with antihypertensive properties. It acts by inhibiting the renal tubular reabsorption of sodium and chloride ions, which are excreted with an accompanying volume of water. Potassium excretion is also promoted.

Amiloride hydrochloride dihydrate is a potassium-sparing diuretic. It also promotes the excretion of sodium and chloride, but it reduces the excretion of potassium.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

About 70% of an oral dose of hydrochlorothiazide is absorbed. It has a plasma half life of 5.6 to 14.8 hours. It is excreted unchanged in the urine. It crosses the placental barrier and is secreted in breast milk.

About 50% of an oral dose of amiloride hydrochloride dihydrate is absorbed. It has a plasma half life of about 6 to 9 hours, but its effects may persist for up to 48 hours after a single dose. It is excreted unchanged in the urine and faeces.

5.3 Preclinical safety data

Not relevant data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Povidone
Maize starch
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate
Colloidal silicon dioxide
Talc
Sunset Yellow FCF E110

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 ˚C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack size of 30 tablets.
PP containers with PE closure. Pack size of 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

MA084/03501

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 08 November 2006
Date of latest renewal: 25 January 2012

10. DATE OF REVISION OF THE TEXT

15/04/2024

For internal use only: mt-spc-milorex-tabs-v05-r01-a0