SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uractonum 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Uractonum 25 mg: Each tablet contains 25 mg of spironolactone.

Excipient with known effect: lactose.
Each 25 mg tablet contains 145.00 mg lactose monohydrate which is equal to 137.76 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Uractonum 25 mg are white, round, flat, scored tablets, with a diameter of 8.5 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

4.2. Posology and method of administration

Posology

Adults

Congestive heart failure

Usual dose - 100 mg/day. In difficult or severe cases the dosage may be gradually increased up to 200 mg/day. When oedema is controlled, the usual maintenance level is 75 mg/day to 200 mg/day.

Severe heart failure in conjunction with standard therapy (New York Heart Association Class III-IV)

Based on the Randomized Spironolactone Evaluation Study (RALES), treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily in patients with a serum potassium ≤5.0 mEq/L and serum creatinine ≤2.5 mg/dL. Patients who tolerate 25 mg once daily may have their dose increased to 50 mg once daily as clinically indicated. Patients who do not tolerate 25 mg once daily may have their dose reduced to 25 mg every other day. See section 4.4 for advice on monitoring serum potassium and serum creatinine.

Hepatic cirrhosis with ascites and oedema

If urinary Na+/K+ ratio is greater than 1.0, 100 mg/day. If the ratio is less than 1.0, 200 mg/day to 400 mg/day. Maintenance dosage should be individually determined.

Malignant ascites

Initial dose usually 100 mg/day to 200 mg/day. In severe cases the dosage may be gradually increased up to 400 mg/day. When oedema is controlled, maintenance dosage should be individually determined.

Nephrotic syndrome

Usual dose – 100 mg/day to 200 mg/day. Spironolactone has not been shown to be anti-inflammatory, nor to affect the basic pathological process. Its use is only advised if glucocorticoids by themselves are insufficiently effective.

Diagnosis and treatment of primary aldosteronism

Spironolactone may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long test: Spironolactone is administered at a daily dosage of 400 mg for 3 to 4 weeks. Correction of hypokalaemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short test: Spironolactone is administered at a daily dosage of 400 mg for 4 days. If serum potassium increases during Spironolactone administration but drops when Spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, Spironolactone may be administered in doses of 100 mg to 400 mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, Spironolactone may be employed for long term maintenance therapy at the lowest effective dosage determined for the individual patient.

Essential hypertension

Usual dose – 50 mg/day to100 mg/day, which for difficult or severe cases may be gradually increased at 2 weekly intervals up to 200 mg/day. Treatment should be continued for 2 weeks or longer since an adequate response may not occur before this time. Dosage should subsequently be adjusted according to the response of the patient.

Elderly

It is recommended that treatment is started with the lowest dose and titrated upwards as required to achieve maximum benefit. Care should be taken in severe hepatic and renal impairment which may alter drug metabolism and excretion.

Paediatric population

Initial daily dosage should provide 1-3 mg of spironolactone per kilogram body weight, given in divided doses. Dosage should be adjusted on the basis of response and tolerance (see sections 4.3 and 4.4).

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

Method of administration

Administration of Uractonum once daily with a meal is recommended.

4.3. Contraindications

Spironolactone is contraindicated in adult and paediatric patients with the following:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute renal insufficiency, significant renal compromise, anuria.
- Addison's disease.
- Hyperkalaemia.
- Concomitant use of eplerenone.

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

Uractonum should not be administered concurrently with other potassium conserving diuretics and potassium supplements should not be given routinely with Uractonum as hyperkalaemia may be induced.

4.4. Special warnings and precautions for use

Concomitant use of spironolactone with other potassium sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other drugs or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium or salt substitutes containing potassium, may lead to severe hyperkalaemia.

Hyperkalaemia may also occur in patients with impaired renal function. Cardiac dysrhythmias, occasionally fatal, may result.

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of those drugs.

Reversible increases in blood urea may occur during use of the drug especially in the presence of impaired renal function.

Dilution hyponatraemia may occur in combination with other diuretics.

Patients who are being treated with this preparation require regular supervision with monitoring of fluid and electrolyte state. Periodic estimation of serum electrolytes is recommended due to the possibility of hyperkalaemia, hyponatremia and possible transient blood urea nitrogen (BUN) elevation, especially in the elderly and/or in patients with pre-existing impaired renal or hepatic function.

The preparation should only be used with particular caution in elderly patients or those with potential obstruction of the urinary tract, or with disorders rendering their electrolyte balance precarious.

Spironolactone may induce gynaecomastia and menstrual irregularities.

Reversible hyperchloraemic metabolic acidosis, usually in association with hyperkalaemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even when renal function is normal.

Carcinogenicity: see section 5.3.

Hyperkalaemia in Patients with Severe Heart Failure

Hyperkalaemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium >3.5 mEq/L. The recommended monitoring for potassium and creatinine is 1 week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium >5 mEq/L or for serum creatinine >4 mg/dL (see section 4.2).

Paediatric population

Potassium-sparing diuretics should be used with caution in hypertensive paediatric patients with mild renal insufficiency because of the risk of hyperkalaemia. (Spironolactone is contraindicated for use in paediatric patients with moderate or severe renal impairment; see section 4.3).

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

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant use of drugs known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia. In addition, concomitant use of trimethoprim/sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

Spironolactone has been reported to increase serum digoxin concentration and to interfere with certain serum digoxin assays. In patients receiving digoxin and spironolactone the digoxin response should be monitored by means other than serum digoxin concentrations, unless the digoxin assay used has been proven not to be affected by spironolactone therapy.
If it proves necessary to adjust the dose of digoxin, patients should be carefully monitored for evidence of enhanced or reduced digoxin effect.

Concurrent use with carbenoxolone or lithium salts should be avoided.

Hyperkalaemic metabolic acidosis has been reported in patients given spironolactone concurrently with ammonium chloride or colestyramine.

Potentiation of the effect of other diuretics and antihypertensive drugs occurs and their dosage may need to be reduced by about 50% when Spironolactone is added to the treatment regime, and then adjusted as necessary. Concomitant administration with cardiac glycosides may necessitate adjustment of the dosages of these drugs.

Since ACE inhibitors decrease aldosterone production they should not routinely be used with Spironolactone, particularly in patients with marked renal impairment.

Non-steroidal anti-inflammatory drugs such as aspirin, indomethacin and mefenamic acid may attenuate the natriuretic efficacy of diuretics due to the inhibition of intra-renal synthesis of prostaglandins and have been shown to attenuate the diuretic effect of spironolactone.

Spironolactone reduces vascular responsiveness to noradrenaline.

Caution should be exercised in the management of patients subjected to regional or general anaesthesia while they are being treated with Spironolactone.

Spironolactone has been shown to increase the half-life of digoxin.

Spironolactone can interfere with assays for plasma digoxin concentrations.

Spironolactone enhances the metabolism of antipyrine.

In fluorimetric assays, spironolactone may interfere with the estimation of compounds with similar fluorescence characteristics.

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels in abiraterone-treated prostate cancer patients. Use with abiraterone is not recommended.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no studies in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). Spironolactone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

The metabolite canrenone is detected in breast milk, so that breast-feeding of infants should be avoided during therapy with the drug.

Fertility

Studies in animals suggest spironolactone may impair fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

4.8. Undesirable effects

The following adverse events have been reported in association with spironolactone therapy:
The following undesirable effects have been observed in clinical trials and reported during treatment with spironolactone with the following frequencies: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Benign breast neoplasm (male)			
Blood and lymphatic system disorders						Agranulocytosis, Leukopenia, Thrombocytopenia, Anaemia, Purpura, Eosinophilia
Metabolism and nutrition disorders	Hyperkalaemia		Electrolyte imbalance			

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Psychiatric disorders		Confusional state				Libido disorder
Nervous system disorders		Dizziness				Headache, Drowsiness, Ataxia, Lethargy
Gastrointestinal disorders		Nausea				Gastrointestinal disorder
Hepatobiliary disorders			Hepatic function abnormal			
Skin and subcutaneous tissue disorders		Pruritus, Rash	Urticaria			Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), Alopecia, Hypertrichosis, Pemphigoid
Musculoskeletal and connective tissue disorders		Muscle spasms				
Renal and urinary disorders		Acute kidney injury				
Reproductive system and breast disorders		Gynaecomastia*, Breast pain**	Menstrual disorder			Impotence
General disorders and		Malaise				Drug fever

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
administration site conditions						

* Gynaecomastia may develop in association with the use of spironolactone. Development appears to be related to both dosage level and duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances some breast enlargement may persist.

** In clinical trials, breast pain was reported more commonly in males than in females.

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 the national reporting system.

4.9. Overdose

Symptoms

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness, diarrhoea or maculopapular or erythematous rash. Dehydration may occur.

Hyponatraemia or hyperkalaemia may be induced but these effects are unlikely to be associated with acute overdosage. Symptoms of hyperkalaemia may manifest as paraesthesia, weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia. Electro-cardiographic changes are the earliest specific signs of potassium disturbance.

Management

No specific antidote has been identified. Spironolactone use should be discontinued. Improvement may be expected after withdrawal of the drug. General supportive measures including replacement of fluids and electrolytes may be indicated. For hyperkalaemia, reduce potassium intake, administer potassium-excreting diuretics, intravenous glucose with regular insulin, or oral ion-exchange resins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: potassium-sparing agents, ATC code C03DA01.

Mechanism of action

Spironolactone, as a competitive aldosterone antagonist, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action, maximum response being usually attained after 2 to 3 days treatment. Combination of Spironolactone with a conventional, more proximally acting diuretic usually enhances diuresis without excessive potassium loss.

Severe Heart Failure

RALES was a multinational, double-blind study in 1663 patients with an ejection fraction of ≤35%, a history of NYHA Class IV heart failure within 6 months, and Class III-IV heart failure at the time of randomization. All patients were required to be taking a loop diuretic and, if tolerated, an ACE inhibitor. Patients with a baseline serum creatinine of >2.5 mg/dL or a recent increase of 25% or with a baseline serum potassium of >5.0 mEq/L were excluded. Patients were randomized 1:1 to spironolactone 25 mg orally once daily or matching placebo. Patients who tolerated 25 mg once daily had their dose increased to 50 mg once daily as clinically indicated. Patients who did not tolerate 25 mg once daily had their dosage reduced to 25 mg every other day. The primary endpoint for RALES was time to all-cause mortality.

RALES was terminated early, after a mean follow-up of 24 months, because of significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death by 30% compared to placebo ($p<0.001$; 95% confidence interval 18% - 40%). Spironolactone reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure by 31% compared to placebo ($p <0.001$; 95% confidence interval 18% - 42%).

Spironolactone also reduced the risk of hospitalization for cardiac causes (defined as worsening heart failure, angina, ventricular arrhythmias or myocardial infarction) by 30% ($p<0.001$ 95% confidence interval 18% - 41%). Changes in NYHA class were more favorable with spironolactone: in the spironolactone group, NYHA class at the end of the study improved in 41% ofpatients and worsened in 38% compared to improved in 33% and worsened in 48% in the placebo group ($p<0.001$).

Paediatric population

There is a lack of substantive information from clinical studies on spironolactone in children. This is a result of several factors: the few trials that have been performed in the paediatric population, the use of spironolactone in combination with other agents, the small numbers of patients evaluated in each trial and the different indications studied. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in scientific literature.

5.2. Pharmacokinetic properties

Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulfur containing metabolites (80%) and partly canrenone (20%). Although the plasma half-life of spironolactone itself is short (1.3 hours) the half-lives of active metabolites are longer (ranging from 2.8 to 11.2 hours).

Paediatric population

There are no pharmacokinetic data available in respect of use in paediatric population. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

5.3. Preclinical safety data

Carcinogenicity

Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150 and 500 mg/kg/day (about 1x, 4x, and 12x, respectively, the maximum human recommended daily dose of 400 mg/day based on body surface area), there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In 24-month studies in which rats were administered doses of about 10, 30, 100, and 150 mg/kg/day of spironolactone (about 0.2x, 0.7x, and 2x, respectively, the maximum recommended daily dose of 400 mg/day based on body surface area), the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant increase in benign uterine endometrial stromal polyps in females.

A dose-related (above 30 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of 1 year. In 2-year studies in the rats, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors.

Genotoxicity

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests in vitro. In the presence of metabolic activation,

spironolactone has been reported to be negative in some mammalian mutagenicity tests in vitro and positive for mutagenicity in other mammalian tests in vitro. In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests in vitro, inconclusive in others, and negative in still others.

Fertility and Reproductive Toxicity

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg/kg/day of spironolactone (about 0.4x and 1x, respectively, the maximum human recommended daily dose of 400 mg/day based on body surface area), there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. Spironolactone was devoid of teratogenic effects in mice. Rabbits receiving spironolactone showed reduced conception rate, increased resorption rate, and lower numbers of live births. No embryotoxic effects were seen in rats administered high dosages, but limited, dosage-related hyprolactinemia and decreased ventral prostate and seminal vesicle weights in males, and increasing luteinizing hormone secretion and ovarian and uterine weights in females were reported. Feminization of the external genitalia of male fetuses was reported in another study in rats. When injected into female rats (100 mg/kg/day for 7 days, i.p.) (about 2x the maximum human recommended daily dose of 400 mg/day based on body surface area), spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a 2-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility and fecundity. Spironolactone (100 mg/kg/day) (about 1x, the maximum human recommended daily dose of 400 mg/day based on body surface area), administered i.p. to female mice during a 2-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg (about 2x, the maximum human recommended daily dose of 400 mg/day based on body surface area) also increased the latency period to mating.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablets also contain lactose, maize starch, croscarmellose sodium, povidone, sodium lauryl sulphate, magnesium stearate and peppermint flavour.

6.2. Incompatibilities

None stated.

6.3. Shelf life

60 months.

6.4. Special precautions for storage

Store below 30°C in the original package.

6.5. Nature and contents of container

Uractonum 25mg tablets:
Blisters of polyvinylchloride and aluminium, of ten tablets. Packs of 20, 50 and 100 are available.
Polypropylene securitainers with polyethylene caps containing 100, 250, 500 or 1000 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBERS

06346/08846/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/07/2021
Date of latest renewal: N/A

10. DATE OF REVISION OF THE TEXT