SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Urospir™ 25 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 25 mg spironolactone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

A clear colourless to pale yellow non aqueous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Congestive cardiac failure
- Hepatic cirrhosis with ascites and oedema
- Malignant ascites
- Nephrotic syndrome
- Diagnosis and treatment of primary aldosteronism.

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

NOTE

Urospir 25 mg/5 ml Oral Solution is only suitable for administration of single doses up to 100 mg (20 ml) and up to 200 mg/day in two equally divided doses (20 ml twice a day). When doses more than 200 mg/day are required, other suitable spironolactone formulations should be used.

Urospir is not bioequivalent to the innovator tablet. Switching between spironolactone tablets or other spironolactone products and this formulation should be avoided if possible. If a switch is necessary, caution and increased clinical supervision are required. Refer to Section 5.2.

Posology

Adults

Congestive cardiac failure with oedema

For management of oedema an initial daily dose of 100 mg (20 ml) of spironolactone administered in either single or divided doses is recommended, but may range from 25 mg (5 ml) to 200 mg daily (20 ml twice a day). Maintenance dose should be individually determined.

Severe heart failure (New York Heart Association Class III-IV)

Based on the Randomized Aldactone Evaluation Study (RALES: see also section 5.1), treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg (5 ml) once daily if serum potassium is ≤5.0 mEq/L and serum creatinine is ≤2.5 mg/dL. Patients who tolerate 25 mg once daily may have their dose increased to 50 mg (10 ml) 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 (20 ml)/day. If the ratio is less than 1.0, 200 mg/day (20 ml twice a day) to 400 mg/day (use a suitable spironolactone formulation; see NOTE above).. Maintenance dosage should be individually determined.

Malignant ascites

Initial dose usually 100 mg (20 ml)/day to 200 mg/day (20 ml twice a day). In severe cases the dosage may be gradually increased up to 400 mg/day (use a suitable spironolactone formulation; see NOTE above). When oedema is controlled, maintenance dosage should be individually determined.

Nephrotic syndrome

Usual dose 100 mg (20 ml)/day to 200 mg/day (20 ml twice a 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. As the tests require daily doses higher than 200 mg, other suitable spironolactone formulations should be used; see NOTE above

Long test: Spironolactone is administered at a daily dosage of 400 mg for 3 to 4 weeks. Correction of hypokalaemia and 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 at doses of 100 mg (20 ml) to 400 mg daily (see NOTE above) 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.

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 with 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 (kg) body weight (0.2 ml/kg-0.6 ml/kg) given in divided doses. Dosage should be adjusted on the basis of response and tolerance (see sections 4.3 and 4.4).

Due to the level of medium chain triglycerides in Spironolactone Oral Solution, it is recommended that doses of 3mg/kg be administered using the 50 mg/5ml Oral Solution.

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

For oral administration.

Administration of spironolactone with a meal is recommended.

For instructions on how to use the device refer to section 6.6.

This product is incompatible with polystyrene or PVC and therefore, other devices may react with the product.

Dosage equivalence for the syringe

Each 1 ml = 5 mg

Measure Amount (ml)	Amount of spironolactone (mg)
0.1 ml	0.5 mg
0.5 ml	2.5 mg
1 ml	5 mg
2.5 ml	12.5 mg
3 ml	15 mg

4.3 Contraindications

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

- acute renal insufficiency, significant renal compromise, anuria
- Addison's disease
- hyperkalaemia
- hypersensitivity to spironolactone or to any of the excipients listed in section 6.1
- concomitant use of eplerenone or other potassium sparing diuretics.

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

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

4.4 Special warnings and precautions for use

Fluid and electrolyte balance

Fluid and electrolyte status should be regularly monitored particularly in the elderly, in those with significant renal and hepatic impairment.

Hyperkalaemia may occur in patients with impaired renal function or excessive

potassium intake and can cause cardiac irregularities which may be fatal. Should hyperkalaemia develop spironolactone should be discontinued, and if necessary, active measures taken to reduce the serum potassium to normal (see section 4.3).

Reversible hyperchloraemic metabolic acidosis, usually in association with

hyperkalaemia has been reported to occur in some patients with decompensated

hepatic cirrhosis, even in the presence of normal renal function.

Concomitant use of spironolactone with other potassium-sparing diuretics, angiotensinconverting 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.

Urea

Reversible increases in blood urea have been reported in association with spironolactone, therapy, particularly in the presence of impaired renal function.

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).

4.5 Interaction 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.

Potentiation of the effect of antihypertensive drugs occurs and their dosage may

need to be reduced when Spironolactone is added to the treatment regime and then adjusted as necessary. Since ACE inhibitors decrease aldosterone production they should not routinely be used with spironolactone, particularly in patients with marked renal impairment.

As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone concurrent use should be avoided.

Non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, and

mefenamic acid may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal 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.

In fluorimetric assays, Spironolactone may interfere with the estimation of

compounds with similar fluorescence characteristics.

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

Spironolactone enhances the metabolism of antipyrine.

Spironolactone can interfere with assays for plasma digoxin concentrations.

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 limited data from the use of spironolactone in pregnant women.

Studies in animals have shown reproductive toxicity associated with the antiandrogenic effect of spironolactone (see Section 5.3).

Diuretics can lead to reduced perfusion of the placenta and thus to impairment of intrauterine growth and are therefore not recommended for the standard therapy for hypertension and oedema during pregnancy.

Spironolactone should not be used during pregnancy, unless the potential benefit justifies the potential risk.

Breast-feeding

Canrenone (a major and active) metabolite of spironolactone, is excreted in human milk. There is insufficient information on the effects of spironolactone in newborns/infants.

Spironolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spironolactone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Spironolactone administered to female mice reduced 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

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 the drug is discontinued. In rare instances some breast enlargement may persist.

The following adverse events have been reported in association with spironolactone therapy:

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

System Organ Class	**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**	**Frequency Not Known (cannot be estimated from the available data)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Benign breast neoplasm (male)			
Blood and lymphatic system disorders						Agranulocytosis, Leukopenia, Thrombocytopenia

Metabolism and nutrition disorders	Hyperkalaemia		Electrolyte imbalance			
Psychiatric disorders		Confusional state				Libido disorder
Nervous system disorders		Dizziness				
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 (male)[a]	Menstrual disorder, Breast pain (female)[b]			
General disorders and administration site conditions		Malaise				

Abbreviations: CDS = Core Data Sheet; F = female; LLT = lower level term; M = male; PT = preferred term; WHO-ART = World Health Organization Adverse Drug Reaction Terminology.

[a]The term Breast pain is mapped from CDS and the frequency is derived from WHO-ART

term Breast pain (M); however, Breast pain male is the LLT.
[b]Breast pain is the PT from CDS, and the frequency is derived from WHO-ART term Breast pain (F).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea. 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. Electrocardiographic changes are the earliest specific signs of potassium disturbances. No specific antidote has been identified. 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.

Clinical efficacy and safety

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 taking a loop

diuretic, 97% were taking an ACE inhibitor and 78% were on digoxin (at the time this trial was conducted, b-blockers were not widely used to treat heart failure and only 15% were treated with a b-blocker). 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 also significantly reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure as well as the risk of hospitalization for cardiac causes. Changes in NYHA class were more favourable with spironolactone. Gynaecomastia or breast pain was reported in 10% of men who were treated with spironolactone, as compared with 1% of men in the placebo group ($p<0.001$). The incidence of serious hyperkalaemia was low in both groups of patients.

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 the 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 the active metabolites are longer (ranging from 2.8 to 11.2 hours). Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (Tmax), peak plasma concentration (Cmax), and elimination half-life ($t_{1/2}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, Tmax was 3.2 hr. and 4.3 hr., Cmax was 391 ng/ml and 181 ng/ml, and $t_{1/2}$ was 13.8 hr. and 16.5 hr., respectively.

Relative bioavailability between 10ml of Spironolactone 50 mg/5 ml oral solution and the 100 mg reference product tablet has been studied in healthy male volunteers under fed conditions. The two formulations were bioequivalent for AUC but the mean Cmax of the oral suspension was 20% lower, and not bioequivalent between test and reference products. Switching between spironolactone tablets or other spironolactone products and this formulation should be avoided if possible. If a switch is necessary, caution and increased clinical supervision are required.

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

Spironolactone has been shown to be tumourigenic in rats when administered at high doses over a long period of time. The significance of these findings with respect to clinical use is not known.

Nonclinical data reveal no evidence of teratogenicity, but embryo-fetal toxicity has been seen in rabbits, and an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development. Endocrine disrupting effects have also been observed in female rodents at clinically relevant exposures. In adult rats, spironolactone was found to increase the length of the estrous cycle, and in female offspring exposed late in pregnancy, endocrine dysfunction persisting to adulthood was observed. In mice spironolactone inhibited ovulation and implantation, thereby decreasing fertility. The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium chain triglycerides

Peppermint oil

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products

This product should not be mixed with water. This is because the medicine is preservative free, and the contents of the bottle should not come into contact with water.

This product is incompatible with polystyrene and PVC.

This product is not currently recommended for administration via enteral

feeding tubes.

6.3 Shelf life

18 months

After first opening: 1 month

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate.

Store in the original packaging (bottle) in order to protect from light.

6.5 Nature and contents of container

Bottle: Amber (Type III glass)

Closure: HDPE, EPE wadded, child resistant closure

Dosing Device (Oral Syringe): Polypropylene body and HDPE plunger with a capacity of 5ml and dosage graduation at every 0.1ml

Bottle Adaptor: Low density polyethylene

Pack size: 150ml

6.6 Special precautions for disposal

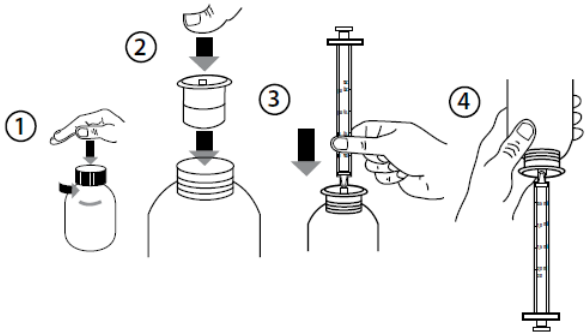
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

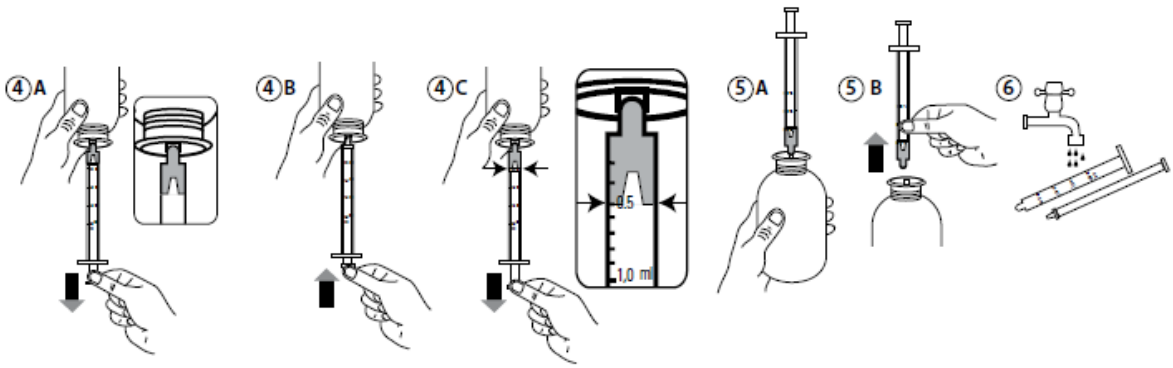
Should a child find the taste unpleasant, the product can be mixed into a small amount of milk, yoghurt or ice cream. Ensure this is taken immediately after its preparation and make sure your child drinks or eats all of it to get the complete dose of medicine.

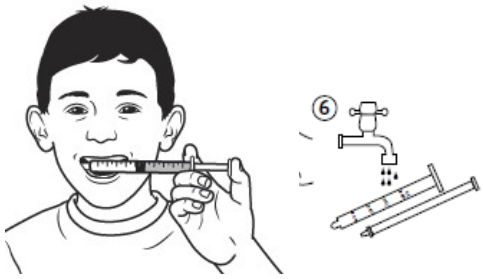
Instructions for use:

- Open the bottle: press the cap and turn it anticlockwise (Figure 1).
- Insert the syringe adaptor into the bottle neck (Figure 2).

- Take the syringe and put it in the adaptor opening (Figure 3).
- Turn the bottle upside down (Figure 4).
- Fill the syringe with a small amount of solution by pulling the plunger down (Figure 4A). Then push the plunger upward in order to remove any possible bubbles (Figure 4B). Finally, pull the plunger down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor. The top flat edge of the plunger should be in line with the graduation mark you are measuring to (Figure 4C).
- Turn the bottle the right way up (Figure 5A).
- Remove the syringe from the adaptor (Figure 5B).
- Put the end of the syringe into your mouth and push the plunger slowly back in to take the medicine.
- **When giving this medicine to a child**:
    - Make sure that your child is sitting up or standing
    - Put the syringe into your child's mouth, placing the barrel-opening in the area between the gums and the inside of the cheek (see Figure 7).
    - Push the plunger slowly, giving your child time to swallow the medicine as it squirts out. Do not push the plunger too quickly as the medicine may come out too quickly and your child may choke.
    - Give your child a drink in order to ensure that all the medicine is washed down
- Wash and dry the syringe before you use it again (Figure 6).
- Close the bottle with the plastic screw cap - leave the syringe adaptor in the bottle.







7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00427/0250

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/07/2024

10 DATE OF REVISION OF THE TEXT

16/07/2024