SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Spironolactone 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of spironolactone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Buff coloured biconvex film coated tablet marked “APS” or plain on one side and “50 0707” on the reverse

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Spironolactone tablets are indicated for the treatment of hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, congestive cardiac failure, 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

Posology

Adults:

Congestive cardiac failure with oedema

For management of oedema an initial dose of 100 mg/day administered in either single or divided doses is recommended but may range from 25 mg to 200 mg daily. The maintenance dose should be individually determined.

Severe heart failure (NYHA Class III-IV)

Treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily if serum potassium is $\leq$ 5.0 mEq/L and serum creatinine is $\leq$ 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.

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 when glucocorticoids alone are insufficiently effective.

Hepatic cirrhosis with ascites and oedema
If the urinary Na^+/K^+ ratio is greater than 1.0 a dosage of 100 mg daily is recommended and if less than 1.0 a daily dosage of 200 - 400 mg. The 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, the maintenance dosage should be individually determined.

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 - 4 weeks. Correction of hypokalaemia and hypertension provides presumptive 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 preparation for surgery at a dosage of 100 - 400 mg daily. For patients who are considered unsuitable for surgery spironolactone may be used for long-term maintenance therapy at the lowest possible 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 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
For oral administration.

Administration of spironolactone once daily with a meal is recommended.

4.3. Contraindications

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

- acute renal insufficiency, significant renal compromise, anuria
- hyperkalaemia
- Addison's disease
- 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 in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

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.

Urea
Spironolactone therapy may cause reversible increases in blood urea, especially in patients with pre-existing renal impairment.

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).

Excipients

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. 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.

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.

Spironolactone may reduce mitotane plasma levels in adrenocortical carcinoma patients treated with mitotane and should not be used concomitantly with mitotane.

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 anti-androgenic 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:

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

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)
Nervous system disorders		Dizziness, Headache, Drowsiness, Lethargy, Ataxia				
Gastrointestinal disorders		Nausea Vomiting, Abdominal pain, Diarrhoea				Gastrointestinal disorder
Hepatobiliary disorders		Hepatotoxicity	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				

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)
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 Organisation 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 symptoms may include 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 disturbance.

There is no specific antidote.

Improvement may be expected after withdrawal of spironolactone. General supportive measures including replacement of fluid 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

ATC Code: C03D A01 (potassium-sparing agents, aldosterone antagonists).

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 randomisation. 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 randomised 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 hospitalisation 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 (t1/2) 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 t1/2 was 13.8 hr. and 16.5 hr., respectively.

The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 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
Spironolactone has been shown to produce tumours 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

The tablet contains:
Colloidal anhydrous silica
Sodium laurilsulfate
Lactose monohydrate

Microcrystalline cellulose (E460)
Sodium starch glycolate
Rice starch
Povidone (E1201)
Peppermint oil
Menthol
Magnesium stearate

The coating contains:
Hypromellose (E464)
Polyethylene glycol
Titanium dioxide (E171)
Iron oxide (E172)
Talc (E553b)

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25ºC. Protect from light.

6.5 Nature and contents of container

Polypropylene containers with polyethylene security closures or HDPE containers with LDPE lids in pack sizes of 100 or 500.

PVdC coated PVC film with hard temper aluminium foil blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0136

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/06/1991

10 DATE OF REVISION OF THE TEXT

13/11/2025