

1.3 Product Information

1.3.1 SPC, labeling and package leaflet

1.3.1.1 Summary of product characteristics

Summary of product characteristics is presented on subsequent pages:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spirolactone Accord 25 mg, film-coated tablets
Spirolactone Accord 50 mg, film-coated tablets
Spirolactone Accord 100 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spirolactone Accord 25 mg, film-coated tablets contain 25 mg spiroolactone
Excipients with known effect: Lactose
Each tablet contains 75 mg lactose monohydrate.

Spirolactone Accord 50 mg, film-coated tablets contain 50 mg spiroolactone
Excipients with known effect: Lactose
Each tablet contains 150 mg lactose monohydrate.

Spirolactone Accord 100 mg, film-coated tablets contain 100 mg spiroolactone
Excipients with known effect: Lactose
Each tablet contains 300 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Spirolactone Accord 25 mg, film-coated tablets are white to pale white, round, biconvex tablets printed with "AD" on one side and no imprint on the other side.
25mg tablet diameter is approximately 8.1 mm.

Spirolactone Accord 50 mg, film-coated tablets are white to pale white, round, biconvex tablets printed with "AE" on one side and no imprint on the other side.
50mg tablet diameter is approximately 10.1 mm.

Spirolactone Accord 100 mg, film-coated tablets are white to pale white, round, biconvex tablets printed with "AF" on one side and no imprint on the other side.
100mg tablet diameter is approximately 11.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Oedema associated with congestive heart failure
- Severe heart failure, (NYHA III-IV)
- As an adjuvant in treatment of resistant hypertension
- Nephrotic syndrome
- Liver cirrhosis with ascites and oedema
- Diagnosis and treatment of primary hyperaldosteronism (Conn's syndrome)

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

The dosage should be determined individually depending on the condition and the degree of diuresis required. Dosage up to 100 mg daily may be administered as a single dose or in divided doses.

Oedema associated with congestive heart failure

For management of oedema an initial daily dose of 100 mg of spironolactone administered in either single or divided doses is recommended, but may range from 25 to 200 mg daily. 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 ≤ 5.0 mEq/L and serum creatinine is ≤ 2.5 mg/dL (221 μ mol/L). 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.

Resistant Hypertension

The starting dose for spironolactone should be 25mg daily in a single dose; the lowest effective dose should be found, very gradually titrating upwards to a dose of 100mg daily or more.

Nephrotic syndrome

Usual dose is 100-200mg/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.

Hepatic cirrhosis with ascites and oedema

The starting dose is 100-200 mg per day, e.g. based on Na⁺/K⁺ ratio. If the response to 200 mg spironolactone within the first two weeks is not sufficient, furosemide is added and if necessary, the spironolactone dose is increased stepwise up to 400 mg per day. Maintenance dosage should be individually determined.

Diagnosis and treatment of primary aldosteronism

If primary hyperaldosteronism is suspected, spironolactone is given at a dose of 100 – 150 mg, or up to 400 mg daily. In the event of rapid onset of a strong diuretic and antihypertensive effect, this is a clear indication of elevated aldosterone production. In this case, 100 – 150 mg daily is administered for 3 – 5 weeks prior to surgery. If surgery is not an option, this dose is often sufficient to maintain blood pressure and potassium concentration at normal levels. In exceptional cases, higher doses are necessary, but the lowest possible dosage should be found.

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). The tablet may be ground or crushed and then suspended in water to make it easier to take. Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

The Elderly

It is recommended that treatment is started at the lowest possible dose, then titrated with higher doses until the optimum effect is achieved. Caution is required, in particular in renal dysfunction.

Method of administration

The tablets should be taken with meals. Daily dosages in excess of 100 mg should be given in several divided doses.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severe renal insufficiency (eGFR <30 mL per minute per 1.73 m²), acute or progressive kidney disease (whether or not this is accompanied by anuria)
- Hyponatraemia
- Hyperkalaemia (serum potassium level > 5.0 mmol/L) at initiation
- Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)

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

4.4 Special warnings and precautions for use

Fluid and electrolyte balance

During long-term therapy with spironolactone, fluid and electrolyte status should be regularly monitored, especially in elderly patients. Administration of spironolactone is not recommended if plasma potassium levels are elevated and contra-indicated in severe renal insufficiency (See Section 4.3) During treatment with spironolactone, severe hyperkalaemia can occur, which may result in cardiac arrest (sometimes fatal) in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements.

Hyperkalaemia may be accompanied by paraesthesia, weakness, mild paralysis or muscle spasms and is difficult to distinguish clinically from hypokalaemia. ECG changes may be the first sign of disturbed potassium balance, although hyperkalaemia is not always accompanied by an abnormal ECG.

Combination with potent potassium-sparing diuretics such as triamterene and amiloride is contra-indicated in order to prevent hyperkalaemia and care should be taken to avoid administration of extra potassium

Impaired renal function

Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. Therefore, these patients should be treated with caution.

Severe hepatic insufficiency

Caution is required in patients with hepatic disorders due to the risk of hepatic coma.

Carcinogenicity

Animal studies have shown that at high doses and after long-term use, spironolactone induces tumours. The significance of these data for clinical application is unclear. However, the benefits of therapy should be weighed against the possible long-term harm before initiating long-term use of spironolactone in

young patients.

Lactose

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

Paediatric population

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

Concomitant use of medicinal products known to cause hyperkalaemia with spiroolactone may result in severe hyperkalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting spiroolactone

Combinations causing hyperkalaemia

Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) is contraindicated because of the risk of hyperkalaemia (see Section 4.3).

The use of ACE inhibitors in combination with spiroolactone may be accompanied by hyperkalaemia, especially in patients with impaired renal function. Concomitant use requires careful dosing and close monitoring of the electrolyte balance.

Spirolactone and ciclosporin coadministration not recommended, as both increase serum potassium level and possible serious life-threatening interactions.

Heparin, low molecular weight heparin:

Concomitant use of spiroolactone with heparin or low molecular weight heparin may lead to severe hyperkalemia. Increased diuresis has been observed during concomitant use of spiroolactone and heparin.

Non-Steroidal Anti-Inflammatory Drugs

Acetyl salicylic acid and indomethacin may attenuate the diuretic action of spiroolactone due to inhibition of intrarenal synthesis of prostaglandins. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.

Interactions affecting other medicinal products

Anti-coagulants

Spirolactone reduces the effect of anticoagulants.

Noradrenalin

Spirolactone reduces the vasoconstrictive effects of noradrenaline.

Anti-hypertensives

Spirolactone can potentiate the effect of antihypertensive agents. The dosage of such drugs, in particular ganglion-blocking drugs, can often be halved when spiroolactone is added to the therapy.

Lithium

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Digoxin

Spirolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity.

Alcohol, barbiturates or narcotics

Potential of orthostatic hypotension may occur.

Cholestyramine

Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spiroolactone concurrently with cholestyramine.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia, may occur.

Other forms of interaction

Ammonium Chloride

Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spiroolactone concurrently with ammonium chloride (e.g. in liquorice).

Plasma Cortisone levels

Spirolactone interferes with Mattingly's fluorimetric method for determination of plasma cortisone levels.

In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim / sulfamethoxazole (co-trimoxazole) with spiroolactone may result in clinically relevant hyperkalaemia

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are very limited data on the use of spiroolactone during pregnancy in humans.

Experimental animal studies have shown reproductive toxicity associated with the anti-androgenic effect of spiroolactone (see section 5.3). Spiroolactone should not be used during pregnancy.

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 edema during pregnancy.

Breastfeeding

Canrenone, the principal and active metabolite of spiroolactone, appears in small quantities in human breast milk. Spiroolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spiroolactone-therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women.

Fertility

Spirolactone may induce impotence and menstrual irregularities (see section 4.8).

4.7 Effects on ability to drive and use machines

No data are available on the ability to drive. Undesirable effects such as dizziness, confusion and headache may occur. The possible occurrence of these undesirable effects should be taken into account when driving or using machines.

4.8. Undesirable effects

The undesirable effects are dependent on dose and duration of treatment.

The most common adverse effects are hyperkalaemia (9%), disorders of the reproductive system and breasts, including gynaecomastia, reported in 13% of patients (at a dose of less than 100 mg). Gynaecomastia appears to be related to both dosage level and duration of therapy and is usually reversible once treatment stops. Other very common undesirable effects include headache, digestive system disorders, diarrhoea, fatigue and drowsiness.

The undesirable effects below are classified in accordance with the following frequencies: Very common ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1,000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1,000$), Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Very rare: breast cancer

Blood and lymphatic system disorders

Rare: thrombocytopenia, eosinophilia, leukopenia (including agranulocytosis)

Immune system disorders

Rare: eczema (type 1 allergic reaction), hypersensitivity

Endocrine disorders

Not known: slight androgenic effects, including hirsutism.

Metabolism and nutrition disorders

Very common: hyperkalaemia in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements (see also section 4.4)

Common: hyponatraemia (in particular during combined intensive therapy with thiazide diuretics), hyperkalaemia in (1) patients with severe renal dysfunction, (2) patients receiving treatment with ACE inhibitors or potassium chloride, (3) the elderly, and (4) diabetic patients

Uncommon: acidity of the blood (acidosis) in patients with liver problems

Rare: insufficient fluid in the tissues (dehydration), porphyria, temporary increase in nitrogen levels in the blood and urine, hyperuricemia (may lead to gout in predisposed patients)

Not known: reversible hyperchloraemic metabolic acidosis – usually accompanied by hyperkalaemia has been reported in some patients with decompensated hepatic cirrhosis, even where renal function was normal.

Psychiatric disorders

Uncommon: confusion

Nervous system disorders

Very common: headache

Common: weakness, lethargy in patients with cirrhosis, tingling (paraesthesia)

Rare: paralysis, paraplegia of the limbs due to hyperkalaemia

Not known: dizziness, ataxia

Vascular disorders

Very rare: inflammation of the vessel walls (vasculitis)

Not known: mild hypotension

Gastrointestinal disorders

Very common: indigestion, diarrhoea

Common: nausea and vomiting

Very rare: gastric inflammation, gastric ulcers, intestinal haemorrhage, cramps

Hepatobiliary disorders

Very rare: hepatitis

Skin and subcutaneous tissue disorders

Uncommon: skin rash, urticaria, erythema, chloasma, pruritus, exanthema

Very rare: alopecia, eczema, erythema annulare centrifugum (EAC), hypertrichosis

Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) , Pemphigoid

Musculoskeletal and connective tissue disorders

Uncommon: muscle spasms, leg cramps

Very rare: systemic lupus erythematosus (SLE), Osteomalacia

Renal and urinary disorders

Uncommon: elevated serum creatinine levels

Very rare: acute renal failure

Reproductive system and breast disorders

Very common: Men: reduced libido, erectile dysfunction, impotence, enlargement of the mammary glands (gynaecomastia);

Women: breast disorders, tenderness of the breasts, menstrual disorders, deepening of the voice (in many cases irreversible)

Common: Women: changes in vaginal secretions, reduced libido, absence of periods (amenorrhoea), post-menopausal bleeding

General disorders and administration site conditions

Very common: fatigue, drowsiness

common: malaise

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 [To be completed nationally].

4.9 Overdose

Overdose can manifest itself in the form of nausea and vomiting, and (more rarely) by drowsiness, confusion, skin rash or diarrhoea.

In addition, infertility can occur at very high doses (450 mg/day).

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.

If electrolyte balance disturbance and dehydration occur, treatment is symptomatic and supportive and may include 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: cardiovascular system, diuretics, potassium-sparing diuretics, aldosterone antagonist.

ATC code: C03DA01

Spirolactone affects the kidney and the adrenal gland (as an antagonist of aldosterone in the renal tubuli and an inhibitor of aldosterone synthesis in high concentrations).

Spirolactone promotes diuresis in patients with oedema or ascites by increasing excretion of sodium in the urine. Potassium loss caused by thiazide diuretics is reduced. It has a gradual and prolonged action. The antihypertensive effect of spiro lactone is based on water and salt depletion.

Severe heart failure: RALES

The Randomized Aldactone Evaluation Study (RALES) was a multinational, double-blind study in 1663 patients with an ejection fraction of $\leq 35\%$, a history of New York Heart Association (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, beta-blockers were not widely used to treat heart failure and only 15% were treated with a beta-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 spiro lactone 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 a significant mortality benefit detected on a planned interim analysis. Spiro lactone reduced the risk of death compared to placebo (mortality spiro lactone 284/841 (35%); placebo 386/822 (46%); Risk reduction 30% ; 95% confidence interval 18% to 40%; $p < 0.001$). Spiro lactone 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.

Paediatric population

There is a lack of substantive information from clinical studies on spiro lactone in children. This is a result of several factors: the few trials that have been performed in the paediatric population, the use of spiro lactone 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

Absorption

Approximately 70% of spiro lactone is absorbed after oral administration. The bioavailability of spiro lactone can be increased if it is taken with food. The clinical relevance of this effect is however not entirely clear. Following the administration of 100 mg of spiro lactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}), peak plasma concentration (C_{max}), and elimination half-life ($t_{1/2}$) for spiro lactone is 2.6 hr., 80ng/ml, and approximately 1.4hr., respectively. For the 7-alpha- (thiomethyl) spiro lactone and canrenone metabolites, t_{max} was 3.2 hr. and 4.3 hr., C_{max} was 391 ng/ml and 181 ng/ml, and $t_{1/2}$ was 13.8 hr. and 16.5 hr, respectively.

Distribution

Both spiro lactone and canrenone are over 90% bound to plasma proteins.

Biotransformation

Spirolactone is extensively metabolised to active metabolites: including thiomethyl- spironolactone and canrenone.

Elimination

The plasma half-life of spironolactone is approximately 1.5 hours, that of 7 α -thiomethyl- spironolactone approximately 9-12 hours and that of canrenone 10-35 hours. Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces. 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

Preclinical data do not add relevant information to that already mentioned in other sections of this SmPC.

Spirolactone 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.

Studies on reproduction toxicity have not shown an increased risk of congenital anomalies, but an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development. There is no confirmation in humans of these possible adverse effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Pregelatinised corn starch

Calcium hydrogen phosphate, anhydrous

Povidone K25

Peppermint oil

Purified talc

Silica, colloidal anhydrous

Magnesium stearate (E470b)

Film coating:

Hypromellose

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 3 years

Bottles: 24 months

in-use shelf-life after first opening: 3 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Tablets are packed in PVC-Aluminium blister pack & HDPE bottle pack

Pack sizes:

Blister pack: 20, 28, 30, 50, 60, 90 and 100 tablets in blister.

HDPE bottle: 250, 500 and 1000 tablets (for hospital or dose dispensing use only).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House, 319 Pinner Road
North Harrow, Middlesex
HA1 4HF, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT