SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Qaialdo 10 mg/ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 10 mg spironolactone.

Each bottle of 150 ml contains 1 500 mg of spironolactone.

Excipients with known effect

This medicine contains 0.75 mg sodium benzoate and 400 mg sucrose in each ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

White to off white viscous oral suspension.

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.

Neonates, children and adolescents 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 with oedema

Usual dose - 100 mg/day. In difficult or severe cases the dose 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 aldactone 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 $\leq$ 5.0 mEq/L and serum creatinine $\leq$ 221 μmol/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.

Hepatic cirrhosis with ascites and oedema

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

Malignant ascites

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

Essential hypertension

Usual dose – 50 mg/day to 100 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. Dose should subsequently be adjusted according to the response of the patient.

Special populations

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 spironolactone metabolism and excretion.

Renal/ hepatic impairment

Patients with mild renal impairment (glomerular filtration rate (GFR) 60 – 90 ml/min) should be started on the lowest dose. Serum potassium levels and renal function should be monitored closely.

Spironolactone is contraindicated in adult patients with severe (GFR < 30 ml/min) renal impairment (see section 4.3).

Spironolactone is contraindicated in paediatric patients with moderate (GFR 30 - < 60 ml/min) to severe (GFR < 30ml/min) renal impairment (see sections 4.3 and 4.4).

Since impaired hepatic function may result in reduced elimination of spironolactone and its metabolites, patients with impaired hepatic function should be started on the lowest dose and titrated slowly. Patients should be monitored for dose related adverse reactions (see section 4.4).

Paediatric population

Initiate treatment with the smallest dose and adjust on the basis of response and tolerance (see sections 4.3 and 4.4).

Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome;

- Neonate: 1-2 mg/kg/daily in 1-2 divided doses.
- Infant or child 1 month to 18 years: 1-3 mg/kg daily in 1-2 divided doses (maximum 200 mg daily).

Primary hyperaldosteronism; resistant ascites.

- Neonate: up to a maximum of 7 mg/kg daily may be used.
- Infant or Child 1 month to 18 years: up to a maximum of 9 mg/kg daily (total maximum 400 mg daily) may be used.

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

The paediatric table below shows, for a range of ages, weight and doses, the dose (mg) to volume (ml) conversion using the two oral syringes.

Table 1: Dose (mg) to volume (ml) conversion using oral syringe. Daily doses are displayed.

Age (Years)	**Weight* (Kg)**	**Dose†**					
		1 mg/kg		**2 mg/kg**		**3 mg/kg**	
		mg	**ml**	**mg**	**ml**	**mg**	**ml**
0	3.3	3.3	0.3	6.6	0.7	9.9	1.0
1 month	4.5	4.5	0.5	9.0	0.9	13.5	1.4
2 month	5.6	5.6	0.6	11.2	1.1	16.8	1.7
3 month	6.4	6.4	0.6	12.8	1.3	19.2	1.9
4 month	7.0	7.0	0.7	14.0	1.4	21.0	2.1
5 month	7.5	7.5	0.8	15.0	1.5	22.5	2.3
6 month	7.9	7.9	0.8	15.8	1.6	23.7	2.4
1.0	9.6	9.6	1.0	19.2	1.9	28.8	2.9
1.5	10.9	10.9	1.1	21.8	2.2	32.7	3.3
2.0	12.2	12.2	1.2	24.4	2.4	36.6	3.7
3.0	14.3	14.3	1.4	28.6	2.9	42.9	4.3
4.0	16.3	16.3	1.6	32.6	3.3	48.9	4.9
5.0	18.3	18.3	1.8	36.6	3.7	54.9	5.5
6.0	20.5	20.5	2.1	41.0	4.1	61.5	6.2
7.0	22.9	22.9	2.3	45.8	4.6	68.7	6.9
8.0	25.4	25.4	2.5	50.8	5.1	76.2	7.6
9.0	28.1	28.1	2.8	56.2	5.6	84.3	8.4

*50^{th} percentile for boys extracted from WHO (0-10 years) growth charts

†Doses less than or equal to 10 mg to be drawn up using the 1 ml oral syringe. Doses greater than 10 mg to be drawn up using the 5 ml oral syringe or a combination of both syringes (shaded cells).

Method of administration

Spironolactone should be taken together with a meal.

This medicinal product is for oral use. The bottle should be shaken thoroughly before use for redispersing the suspension.

Two dosing syringes (a 1 ml syringe and a 5 ml syringe) are provided for accurate measurement of the prescribed dose of the oral suspension.

The **smaller** 1 ml syringe is for measuring doses of less than or equal to 10 mg. The syringe is marked at 0.1 ml intervals, allowing for dosing in 1 mg increments.

The **larger** 5 ml syringe is for measuring doses more than 10 mg. The syringe has graduations at every 0.2 ml (2 mg) and is marked at 1 ml intervals and at 2.5 ml. Each 1 ml contains 10 mg of spironolactone.

The healthcare professional should advise the patient or carer which syringe to use to ensure that the correct volume is administered.

The healthcare professional should advise the patient or carer to place the tip of the syringe into the mouth and to the inside of the cheek, and the contents gently released. To assist accurate and consistent dose delivery to the stomach, water should be taken after each dose of spironolactone.

In adults without swallowing difficulties, solid oral formulations may be more appropriate and convenient.

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, severe renal impairment (GFR < 30 ml/min), anuria
- Addison's disease
- Hyperkalaemia (> 5.5 mEq/L)
- Concomitant use of eplerenone.

Spironolactone is contraindicated in paediatric patients with moderate (GFR 30 - < 60 ml/min) to severe renal impairment (GFR < 30 ml/min).

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

Monitoring fluid and electrolyte state

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.

Concomitant use of spironolactone with other potassium sparing diuretics, angiotensin- converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory medicinal products, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other medicinal products or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalaemia (see section 4.5).

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

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.

Dilution hyponatraemia may occur in combination with other diuretics (see section 4.5).

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 > 353 μmol/L (see section 4.2).

Concomitant use with cardiac glycosides or hypotensive agents

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of those medicinal products (see section 4.5).

Urea

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

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 with known effect

Sodium benzoate

This medicinal product contains 0.75 mg sodium benzoate in each 1 ml which is equivalent to 112.5 mg/150 ml. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

Sodium

This medicinal product contains less than 1 mmol (23 mg) sodium within the recommended dose range, that is to say essentially 'sodium-free'.

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. As this medicinal product contains 400 mg sucrose per ml, this has to be taken into consideration in terms of daily intake. This should be taken into account in patients with diabetes mellitus. Qaialdo 10 mg/ml may be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting the use of this medicinal product

Interactions affecting the potassium homeostasis

Concomitant use of medicinal products known to cause hyperkalaemia (such as lisinopril, valsartan, indometacin) with spironolactone may result in severe hyperkalaemia.

In addition, concomitant use of trimethoprim/sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

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

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

Interactions attenuating the natriuretic effect of spironolactone

Non-steroidal anti-inflammatory medicinal products such as acetylsalicylic acid, indometacin 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.

Interactions affecting the use of other medicinal products

Concurrent use with carbenoxolone or lithium salts should be avoided.

Lithium

Spironolactone reduces the renal clearance of lithium, thus increasing the risk of lithium toxicity. Monitor lithium levels periodically when spironolactone is coadministered.

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.

Potentiation of the effect of other diuretics and antihypertensive medicinal products occurs and their dose 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 doses of these medicinal products.

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

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 enhances the metabolism of antipyrine.

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

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.

Qaialdo is not recommended during pregnancy and in women of childbearing potential not using contraception.

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.

Qaialdo 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

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

Summary of the safety profile

The most frequent adverse reactions of spironolactone include: hyperkalaemia, reported in 17.5% of patients, particularly in patients with renal impairment or if receiving ACE-inhibitors or angiotensin II antagonists concomitantly; gynaecomastia and breast pain, reported in 9% of males.

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). Table 2 presented below is according to the MedDRA system organ classification and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Tabulated list of adverse reactions

System organ class	**Frequency**	**Adverse reactions**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	Benign breast neoplasm (male)
Blood and lymphatic system	Not known	Leukopenia, Agranulocytosis, Thrombocytopenia, Anaemia, Eosinophilia

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

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

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

*** Arrhythmia, chest pain, nausea, diarrhoea, 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.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be similar to adults.

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 Yellow Card Scheme

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

4.9 Overdose

Symptoms

Acute overdose 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 overdose. See section 4.8 for the symptoms of hyperkalaemia.

Treatment

No specific antidote has been identified. Spironolactone use should be discontinued. Improvement may be expected after withdrawal of the medicinal product. 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: diuretics, aldosterone antagonists and other 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.

Clinical efficacy and safety

Severe heart failure

RALES was a multinational, double-blind study in 1 663 patients with an ejection fraction of ≤ 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 randomization. All patients were required to be taking a loop diuretic and, if tolerated, an ACE inhibitor. Patients with a baseline serum creatinine of > 221 μmol/L 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 dose 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 favourable with spironolactone: In the spironolactone group, NYHA class at the end of the study improved in 41% of patients 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 dose 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 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 dose 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 tumours 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 leukaemia 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 leukaemia and hepatic, thyroid, testicular and mammary tumours.

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 doses, but limited, dose-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

Sodium benzoate (E 211)

Sucrose

Sodium citrate (E 331)

Citric acid monohydrate (E 330)

Strawberry flavour liquid

Masking flavour

Polysorbate 80 (E 433)

Simeticone emulsion 30%

Xanthan gum (E 415)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 2 years

After first opening: Keep the bottle tightly closed and store below 25°C. Discard any unused contents after 12 weeks.

6.4 Special precautions for storage

Before first opening, this medicinal product does not require any special storage conditions.

For storage conditions after first opening, see section 6.3.

6.5 Nature and contents of container

Amber type III glass bottle with tamper evident child-resistant closure (high density polyethylene-HDPE with expanded polyethylene liner) containing 150 ml of oral suspension.

Each pack contains one bottle, a low density polyethylene (LDPE) bottle adaptor and 2 dosing syringes (a 1 ml syringe graduated in 0.01 ml increments and a 5 ml syringe graduated in 0.2 ml increments).

6.6 Special precautions for disposal

The bottle should be shaken thoroughly before use to ensure the oral suspension is well mixed.

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

7 MARKETING AUTHORISATION HOLDER

Nova Laboratories Limited

Martin House, Gloucester Crescent

Wigston, Leicester

LE18 4YL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 13581/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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