IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0936/015/002
Case No: 2043911

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pharmacia Ireland Limited

9 Riverwalk, National Digital Park, **Citywest Business Campus**, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Aldactide 50mg/50mg Film-coated tablets.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/05/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aldactide 50mg/50mg Film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg spironolactone and 50mg hydroflumethiazide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Circular, biconvex, buff coloured, film-coated tablet with a peppermint odour, engraved ‘SEARLE 180’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension and for the control of oedema in congestive cardiac failure.

4.2 Posology and method of administration

Administration of Aldactide once daily with a meal is recommended.

Adults
Essential hypertension: One to two Aldactide 50 tablet with breakfast or the first main meal of the day. Treatment should be continued for at least two weeks to ensure an adequate response to therapy. Dose should be individually determined.

Congestive cardiac failure: Most patients will require an initial dosage of two Aldactide 50 tablets daily. The dosage should be adjusted as necessary and may range from one Aldactide 25 tablet to two Aldactide 50 tablets daily. Treatment should be continued for at least two weeks to ensure an adequate response to therapy. Dose should be individually determined.

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.

Children
Although clinical trials using Aldactide have not been carried out in children, as a guide, a daily dosage providing 1.5 to 3mg of spironolactone per kilogram body weight given in divided doses, may be employed. Dosage should be adjusted on the basis of response and tolerance.

4.3 Contraindications

Aldactide is contraindicated in neonates and young infants, in patients with anuria, acute renal insufficiency, rapidly deteriorating or severe impairment of renal function, hyperkalaemia, precoma associated with severe liver disease, Addison's disease,significant hypercalcemia, and in patients who are hypersensitive to spironolactone, thiazide diuretics or to other sulphonamide derived drugs.

Aldactide should not be administered with other potassium conserving diuretics such as triameterene or amiloride and potassium supplements should not be given routinely with Aldactide as hyperkalemia may be induced.

4.4 Special warnings and precautions for use

Concomitant use of spironolactone with angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, aldosterone blockers, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalaemia.

Hyperkalaemia may also occur in patients with impaired renal function and can cause cardiac irregularities which may be fatal. Should hyperkalaemia develop Aldactide should be discontinued, and if necessary, active measures taken to reduce the serum potassium to normal.

Sulphonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

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 hypokalaemia or hyperkalaemia, hypochloremic alkalosis, or hyponatremia and possible transient BUN elevation, especially in the elderly and/or in patients with pre-existing impaired renal or hepatic function, in patients receiving digoxin and drugs with pro-arrhythmic effects, and in those with potential obstruction of the urinary tract, or with disorders rendering their electrolyte balance precarious.

Hypokalaemia may develop as a result of profound diuresis, particularly when Aldactide is used concomitantly with loop diuretics, glucocorticoids or ACTH.

Hyponatraemia may be induced especially when Aldactide is administered in combination with other diuretics.

The preparation may induce hyperglycaemia particularly in patients with diabetes, and may necessitate adjustment of control by hypoglycaemic agents in cases of diabetes mellitus.

Hepatic impairment: Caution should be observed in patients with acute or severe liver impairment as vigorous diuretic therapy may precipitate encephalopathy in susceptible patients. Regular estimation of serum electrolytes is essential in such patients.

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.

Urea and uric acid: Reversible increases in blood urea have been reported, particularly accompanying vigorous diuresis or in the presence of impaired renal function.

Thiazides may cause hyperuricaemia and precipitate attacks of gout in some patients. Dosage adjustment of anti-gout medications may be necessary.

Hyperlipidaemia: Caution should be observed as increases in cholesterol and triglyceride levels may be associated with thiazide therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Aldactide may have an additive effect when given concomitantly with other diuretics and antihypertensive agents. The dose of such drugs may need to be reduced when Aldactide is added to the treatment regime and then adjusted as necessary. Concomitant use of spironolactone with angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, aldosterone blockers, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe 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 thedigoxin 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.

Coadministration of spironolactone with carbenoxolone may result in decreased efficacy of either agent.

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

Spironolactone and thiazides may reduce 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 Aldactide.

Colestyramine and colestipol reduce the absorption of thiazides and may reduce their diuretic effects.

Thiazide diuretic agents reduce lithium renal clearance and increase the risk of toxicity. Lithium dose adjustment may be required.

Thiazides may increase responsiveness to skeletal muscle relaxants (e.g. tubocurarine).

Non-steroidal anti-inflammatory drugs may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins.

Aspirin, indometacin and mefenamic acid have been shown to attenuate the diuretic effect of spironolactone.

Spironolactone enhances the metabolism of antipyrine.

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

4.6 Pregnancy and lactation

Pregnancy
Spironolactone or its metabolites may cross the placental barrier. Spironolactone was devoid of teratogenic effects in mice. Rabbits receiving spironolactone showed reduced conception rate, increased resorption rate, and lower number of live births. No embryotoxic effects were seen in rats administered high dosages, but limited, dosage-related hypoprolactinemia and decreased ventral prostate and seminal vesicle weights in males, and increased 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.

Thiazides cross the placental barrier. Thiazides may decrease placental perfusion, increase uterine inertia, and inhibit labour.

There are no studies in pregnant women.

The use of Aldactide in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus. These hazards include foetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have been reported in adults.

Lactation
Metabolites of spironolactone and hydroflumethiazide, have been detected in breast milk. If use of Aldactide is considered essential, an alternative method of infant feeding should be instituted.

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

Adverse Events
The following adverse events have been reported in association with spironolactone and spironolactone/thiazide therapy:
Body as a Whole: anaphylactoid reaction, asthenia, fever, malaise, orthostatic hypotension

Endocrine Disorders: benign breast neoplasm, breast pain

Gastrointestinal Disorders: abdominal pain, diarrhoea, gastrointestinal disturbance, nausea, vomiting

Hematologic Disorders: blood dyscrasias, leukopenia (including agranulocytosis), thrombocytopenia, purpura, aplastic anaemia

Liver Disorders: hepatic function abnormal, pancreatitis, jaundice

Metabolic and Nutritional Disorders: electrolyte disturbances, hyperkalemia, raised serum lipids

Musculoskeletal Disorders: leg cramps, muscle cramps, necrotizing vasculitis

Nervous System Disorders: dizziness, headache, paresthesia, drowsiness, lethargy, restlessness, xanthopsia

Psychiatric Disorders: changes in libido, confusion, ataxia, impotence

Reproductive Disorders: menstrual disorders, mild androgenic effects

Skin and Appendages: alopecia, dermatitis, hypertrichosis, photosensitivity, pruritus, rash, urticaria

Urinary System Disorders: acute renal failure

Gynecomastia may develop in association with the use of spironolactone. Development of gynecomastia is related to both dose and duration of therapy. Gynecomastia is usually reversible when spironolactone is discontinued, although in rare instances some breast enlargement may persist.

Sulfonamide derivatives, including thiazides, have been reported to exacerbate or activate systemic lupus erythematosus.

Rarely hypercalcaemia has been reported in association with thiazides, usually in patients with pre-existing metabolic bone disease or parathyroid dysfunction.

4.9 Overdose

Acute overdosage may be manifested by drowsiness, mental confusion, maculopapular orerythematous rash, nausea, vomiting, dizziness or diarrhoea. Electrolyte imbalance and dehydration may occur. If digitalis has been administered, hypokalaemia may accentuate cardiac arrythmias. Hyponatraemia, hypokalaemia or hyperkalaemia may be induced but these effects are unlikely to be associated with acute overdosage. Symptoms of hyperkalaemia may manifest as paraesthesia, weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia. Electro-cardographic changes are the earliest specific signs of potassium disturbances. No specific antidote has been identified. Aldactide use should be discontinued and potassium intake (including dietary sources) restricted. Improvement may be expected after withdrawal of the drug. General supportive measuresincluding replacement of fluids and electrolytes may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic code: Aldosterone Antagonist and Thiazide Diuretic
ATC Code: C03DA01 + C03AA02

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.

The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 hours.

Hydroflumethiazide is a thiazide diuretic. Diuresis is initiated usually within 2 hours and lasts for about 12-18 hours.

5.2 Pharmacokinetic properties

Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulphur 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).

Hydroflumethiazide is incompletely but fairly rapidly absorbed from the gastro-intestinal tract. It appears to have a biphasic biological half-life with an estimated alpha-phase of about 2 hours and an estimated beta-phase of about 17 hours; it has a metabolite with a longer half-life, which is extensively bound to the red blood cells. Hydroflumethiazide is excreted in the urine; its metabolite has also been detected in the urine.

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. In man and the rat spironolactone is metabolised to a minor extent to canrenone. In contrast canrenone and canrenoic acid are the major metabolites of potassium canrenoate.
A dose related incidence of myelocytic leukaemia has been observed in rats administered potassium canrenoate at doses above 20mg/kg/day for a period of one year. In one long term (two year) oral carcinogenicity study of potassium canrenoate in the rat, myelocytic leukaemia and hepatic, thyroid, testicular and mammary tumours were observed. Potassium canrenoate was not mutagenic in tests using bacteria and yeast, or in an in vivo mammalian system.

It was mutagenic in in vitro tests in mammalian cells following metabolic activation. An increased incidence of leukaemia has not been observed in chronic rat toxicity studies with spironolactone at doses up to 500mg/kg/day, which may be due to differences in metabolism between spirolactone and potassium canrenoate in rats.

The usual therapeutic dose of spironolactone ranges between 0.35 to 5.7mg/kg/day (25-400mg/day). The significance of these animal findings with respect to clinical use is not certain. However, the long term use of spironolactone in young patients requires careful consideration of the benefits and the potential hazard involved.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium sulphate dihydrate
Maize starch
Povidone
Magnesium stearate
Peppermint flavour
Hypromellose
Macrogol 400
Opaspray yellow contains:
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Hypromellose 5cP (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.
Keep container in the outer carton.

6.5 Nature and contents of container

HDPE containers or PVC/foil blister packs containing 100 and 500 tablets. PVC/foil blister calendar pack of 28 tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmacia Ireland Limited
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0936/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 May 1978

Date of last renewal: 30 May 2008

10 DATE OF REVISION OF THE TEXT

January 2010