SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Spiromide Tablets

2. Qualitative and quantitative composition

Each Film Coated Tablet contains:

Spironolactone 50mg

Furosemide ...20mg

3. Pharmaceutical form:

Film Coated Tablets

4. Clinical particulars:

4.1. Therapeutic indications:

Edematous conditions especially those in which secondary hyperaldosteronism is involved: edema and ascites of congestive heart failure and cirrhosis of the liver. SPIROMIDE is also indicated in the management of mild to moderate hypertension and the nephritic syndrome.

4.2. Posology and method of administration:

For oral administration.

From one to four tablets daily (50 to 200 mg of spironolactone and 20 to 80 mg of Furosemide) according to the patient's response..

4.3. Contraindications

Acute renal insufficiency, significant deterioration of renal function, anuria, hyperkalemia, and in patients with a history of hypersensitivity to Furosemide or Spironolactone.

4.4. Special warnings and precautions for use:

An adjustment in the dosage of cardiac glycosides and anti hypertensive drugs may be necessary when Spiromide is added to the regimen.

The administration of potassium supplements or other potassium sparing agents is not recommended as they may induce hyperkalemia.

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

4.5. Interaction with other medicinal products and other forms of interaction

Spironolactone

Aspirin: Aspirin reduces urinary excretion of canrenone

Digoxin

Patients taking both patients taking both spironolactone and digoxin show an increase in plasma digoxin

Other Drugs:

Combination of ACE inhibitors, amiloride, triamterene and carbenoxolone should be avoided.

Furosemide

Potentially Hazardous Interactions:

Furosemide is often administered concomitantly with other drugs, particularly in the elderly, and a number of important interactions have been described.

Cardiac Glycosides:

Furosemide induced hypokalemia may increase the incidence of premature beats during treatment with cardiac glycosides.

Aminoglycosides:

The drug may increase the ototoxic effects of aminoglycoside anti biotics.

Cephalosporins:

Nephrotoxicity caused by cephalosporons, such as Cephalosporins may be accentuated by Furosemide.

Lithium:

Due to diurectic induced sodium depletion, lithium excretion is slowed. This in turn may cause elevation of plasma lithium concentrations and results in serious lithium toxicity.

Non Steroidal Anti inflammatory effects:

These drugs tend to cause salt and water retention and may partially antagonize the action of Furosemie.

Corticosteroids:

Fluid retention caused by Steroids may partially antagonize the diuretic effect but potentiate potassium loss.

Angiotensin converting enzyme inhibitors :

Severe hypertension and/or renal failure may occur if patients who are already being treated with high doses of loop diuretics are started on an ACE inhibitor, even in low doses.

Other Significant Interactions:

Analgesics causing sodium retention decrease the natriuretic action of furosemide

4.6. Pregnancy and lactation:

Pregnancy:

Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, furosemide crosses the placental barrier.

Spironolactone or its metabolites may cross the placental barrier. Animal studies have shown feminisation of the genitalia in male offspring. Anti-androgenic effects have been reported in humans with the risk of ambiguous external genitalia in male newborns (see section 4.3).

Spiromode must not be used in pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Lactation:

Furosemide passes into breast milk and may inhibit lactation. Canerone, a metabolite of spironolactone, appears in breast milk and Spiromode must therefore not be used in breast-feeding mothers.

4.7. Effects on ability to drive and use machines

Reduced mental alertness may impair the ability to drive or operate dangerous machinery. This applies especially at the commencement of treatment.

4.8. Undesirable effects

Frequencies for the following adverse reactions are not known (cannot be estimated from available data):

Furosemide is generally well tolerated.

Blood and lymphatic system disorders

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop. Eosinophilia is rare.

Nervous system disorders

Rarely, paraesthesiae may occur.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.

Renal and urinary disorders

Serum calcium levels may be reduced; in very rare cases tetany has been observed. Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur for example, in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra.

Ear and labyrinth disorders

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.

Vascular disorders

Furosemide may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.

Hepato-biliary disorders

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Skin and subcutaneous tissue disorders

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever or interstitial nephritis, is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, purpura, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).

Metabolism and nutrition disorders

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy.

Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular, calcium and magnesium) is increased. The two active ingredients exert opposing influences on potassium excretion. The serum potassium concentration may decrease, especially at the commencement of treatment (owing to the earlier onset of action of furosemide), although particularly as treatment is continued, the potassium concentration may increase (owing to the later onset of action of spironolactone), especially in patients with renal failure.

Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses. Warning signs of electrolyte disturbances include increased thirst, headache, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. In the event of an irregular pulse, tiredness or muscle weakness (e.g., in the legs), particular consideration must be given to the possibility of hyperkalaemia. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment. Pseudo-Bartter syndrome may occur in the context of misuse and/or long-term use of furosemide.

Disturbances in electrolyte balance, particularly if pronounced, must be corrected.

The diuretic action may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients. Dizziness or leg cramps in the context of hypovolaemia, dehydration or hyperkalaemia may also occur.

To avert these, it is important to compensate any undesired losses of fluid (e.g., due to vomiting or diarrhoea, or to intense sweating). Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long-term therapy they will usually return to normal within six months.

Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

Immune system disorders

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

Gastro-intestinal disorders

Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.

Spironolactone has been reported to induce gastrointestinal intolerance. Stomach ulcers (sometimes with bleeding) have been reported rarely. Spironolactone may also cause drowsiness, headache, ataxia and mental confusion.

Reproductive system and breast disorders

Because of its chemical similarity to the sex hormones, spironolactone may make the nipples more sensitive to touch. Dose dependent mastodynia and reversible gynaecomastia may occur in both sexes. Maculopapular or erythematous cutaneous eruptions have been reported rarely, as have mild androgenic manifestation such as hirsutism and menstrual irregularities. In men, potency may occasionally be impaired.

If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Respiration, thoracic and mediastinal disorders

Rarely, spironolactone may cause vocal changes in the form of hoarseness and (in women), deepening of the voice or (in men) increase in pitch. In some patients these vocal changes persist even after Spiromode has been discontinued.

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.

4.9. Overdose

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body (e.g., hyperkalaemia), this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures (e.g., to promote potassium elimination).

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: low-ceiling diuretic, ATC code: C03AA02

Pharmacotherapeutic group: potassium-sparing agents, ATC Code C03DA01

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.

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

Mechanism of action: it is a combination of two diuretic agents with different but complementary mechanisms and sites of action, thereby providing additive diuretic and antihypertensive effects. Additionally, the spironolactone component helps to minimize the potassium loss characteristically induced by the thiazide component.

The diuretic effect of spironolactone is mediated through its action as a specific pharmacologic antagonist of aldosterone, primarily by competitive binding to receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule

5.2. Pharmacokinetic properties

No pharmacokinetic studies have been performed on spironolactone/ Furosemide. Pharmacokinetic studies have been performed on the individual component of spironolactone and furosemide.

Absorption

Spironolactone

Following oral administration of 500 mg tritiated spironolactone in five healthy male volunteers (fasting state), the total radioactivity in plasma reached a peak between 25 – 40 minutes. Although the absolute bioavailability of spironolactone was not determined, the extent of absorption was estimated to be 75%, as 53% of the dose was excreted in the urine during 6 days and approximately 20% in the bile.

Following oral administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}) and peak plasma concentration (C_{max}) were 2.6 hr. and 80 ng/ml, respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, t_{max} values were 3.2 hr. and 4.3 hr., respectively; C_{max} values were 391 ng/ml and 181 ng/ml, respectively.

Administration with food resulted in higher exposure compared to fasted conditions. Following a single oral dose of 200 mg spironolactone to four healthy volunteers, the mean (± SD) AUC (0 to 24 hours) of the parent drug increased from 288 ± 138 (empty stomach) to 493 ± 105 ng · ml^{-1}· hr (with food) ($p < 0.001$).

Distribution

Spironolactone

Approximately 90% of spironolactone was protein bound based on equilibrium dialysis.

Furosemide

In plasma, furosemide is extensively bound to proteins, mainly to albumin. The volume of distribution of furosemide ranges between 170 and 270 ml.kg.

Biotransformation

Spironolactone

Spironolactone is metabolized by both the kidneys and liver. Following deacetylation and S-methylation, spironolactone is converted to 7-α-thiomethylspironolactone, a sulfur-containing active metabolite which is considered the major metabolite of spironolactone in serum. Approximately 30% of spironolactone is also converted to canrenone by dethioacetylation (non-sulfur containing active metabolite).

Furosemide

In humans, furosemide is partly metabolized to a glucuronide conjugate, which in turn is excreted in urine and bile. The percentage of the dose excreted in urine as the glucoronide conjugate is 7-15%. The glucoronide is inactive.

Elimination

Spironolactone

Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

In one pharmacokinetic study in five healthy male volunteers receiving 500 mg of spironolactone, 53% (range 47-57%) of the dose was excreted in the urine within 6 days and the remaining amount could be detected in the faeces (total recovery 90%). In another study of 5 healthy men, a single dose of spironolactone 200 mg (with radioactive tracer) was administered and in 5 days, 31.6 ± 5.87% of the radioactivity was excreted in the urine mainly as metabolites and 22.7 ± 14.1% in the faeces.

Following oral administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, elimination half-life ($t_{1/2}$) value for spironolactone was 1.4 hr. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, $t_{1/2}$ values were 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

Furosemide

Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

Special Populations

No pharmacokinetic studies have been performed with spironolactone/Furosemide in the elderly or paediatric population or in patients with hepatic or renal insufficiency.

5.3. Preclinical safety data:

Spironolactone

Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in Sprague Dawley 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, 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 a 24-month study using doses of about 10, 30, and 100 mg/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females.

In a 12-month study dietary study in rats with potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) a dose-related (above 30 mg/kg/day) incidence of myelocytic leukemia was observed for a period of one year. In 2 year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors.

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 and canrenoate have been found to be mutagenic, inconclusive or negative in mammalian tests in vitro. In vivo, neither spironolactone nor potassium canrenoate were found to be genotoxic.

Spironolactone has known endocrine effects in animals including progestational and antiandrogenic effects. In a continuous breeding study there was a small increase in incidence of stillborn pups but no effects on mating and fertility at 500 mg spironolactone /kg/day. In female rats treatment with spironolactone for 7 days (100 mg/kg i.p), 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 due to retarded ovarian follicle development and a reduction in circulating oestrogen levels. In female mice spironolactone dosed i.p, caused a decrease in the number of mated mice that conceived and a decreased in the number of implanted embryos in those that became pregnant at dosesof 100 mg/kg/day and also increased the latency period to mating at 200 mg/kg. These effects are associated with an inhibition of ovulation and implantation.

No teratogenic or other embryo-toxic effects were observed in mice at doses up to 20 mg/kg however, this dose caused an increased rate of resorption and a lower number of live foetuses in rabbits. On a body surface area basis, 20 mg/kg is either substantially below or approximate to the maximum recommended human dose in mice and rabbits respectively. Because of its anti-androgenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis. Following administration of 200 mg/kg/day in rats on gestation days 13 to 21, feminization of male foetuses was observed. Dose dependent changes to the reproductive tract that persisted into adulthood including decreases in weights of the ventral prostate and seminal vesicle in males, increased ovary and uterus weights in females, and other indications of endocrine dysfunction were seen in offspring exposed to Spironolactone during late pregnancy at 50 and 100 mg/kg/day.

6. Pharmaceutical particulars

6.1. List of excipients

Corn Starch, Lactose Monohydrate, PolyvinylPyrolidone (K 30), Magnesium Stearate

Coating Ingredient:

Talcum Powder, Titanium Dioxide, HPMC 6cps, PEG 400, PEG 6000, Red Iron Oxide, Isopropyl Alcohol, Purified Water

6.2. Incompatibilities

None stated

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30 ^{0}C. Protect from moisture, freezing, excessive heat and sunlight.

6.5. Nature and contents of container

Alu.Pvc Blisters

6.6. Special precautions for disposal and other handling

There are no specific instructions for use/handling.

Store below 30 ^{0}C.

7. Marketing Authorisation Holder:

The Searle Company Limited
1st Floor, N.I.C.L. Building, Abbasi Shaheed Road,
P. O. Box. 5696, Karachi – 75530,
Pakistan

8. Marketing authorisation number(s):

011024

9. Date of first authorisation/renewal of the authorisation:

May 16, 1995