

Summary of Product Characteristics

1. Name of the medicinal product:

SPIROMIDE

2. Qualitative and quantitative composition

Each tablet contains:

Spironolactone (B.P)50 mg

Furosemide (Ph. Eur.)20 mg

Excipient with known effect: Lactose

For a full list of excipients, see Section 6.1.

3. Pharmaceutical form

Tablets

Pink colored, biconvex film-coated tablets engraved "SEARLE" on one side with a break line another side

4. Clinical particulars

4.1 Therapeutic indications

Spiromide contains a short-acting diuretic and a long-acting aldosterone antagonist. It is indicated in the treatment of resistant oedema where this is associated with secondary hyperaldosteronism; conditions include chronic congestive cardiac failure and hepatic cirrhosis.

Treatment with Spironolactone & Furosemide combination should be reserved for cases refractory to a diuretic alone at conventional doses.

This fixed ratio combination should only be used if titration with the component drugs separately indicates that this product is appropriate.

The use of Spironolactone & Furosemide combination in the management of essential hypertension should be restricted to patients with demonstrated hyperaldosteronism. It is recommended that in these patients also, this combination should only be used if titration with the component drugs separately indicates that this product is appropriate.

4.2 Posology and method of administration

The dose must be the lowest that is sufficient to achieve the desired effect.

Adults: 1-4 Tablets daily.

Children: The product is not suitable for use in children.

Elderly: Furosemide and Spironolactone may both be excreted more slowly in the elderly.

Method of administration

Tablets are best taken at breakfast and/or lunch with a generous amount of liquid (approx. 1 glass). An evening dose is not recommended, especially during initial treatment, because of the increased nocturnal output of urine to be expected in such cases.

4.3 Contraindications

Patients with hypovolemia or dehydration (with or without accompanying hypotension). Patients with an impaired renal function and a creatinine clearance below 30ml/min per 1.73 m² body surface area, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma, hyperkalaemia, severe Hypokalaemia severe hyponatremia, Addison's disease, during pregnancy and breast-feeding women.

Hypersensitivity to furosemide, spironolactone, sulphonamides or sulphonamide derivatives, or any of the excipients of Spironolactone, furosemide.

4.4 Special warnings and precautions for use

Spironolactone may cause vocal changes. In determining whether to initiate treatment with Spiromide, special attention must be given to this possibility in patients whose voice is particularly important for their work (e.g., actors, singers, teachers).

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute retention and require careful monitoring.

Where indicated, steps should be taken to correct hypotension or hypovolemia before commencing therapy.

Particularly careful monitoring is necessary in:

- patients with hypotension.
- patients who are at risk from a pronounced fall in blood pressure.
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- patients with gout.
- patients with hepatic cirrhosis together with impaired renal function.
- patients with hypoproteinemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Administration of Spiromide should be avoided in the presence of a raised serum potassium.

Concomitant administration of triamterene, amiloride, potassium supplements or non-steroidal anti-inflammatory drugs is not recommended as hyperkalaemia may result.

Caution should be observed in patients liable to electrolyte deficiency. Regular monitoring of serum sodium, potassium, creatinine and glucose is generally recommended during therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Spiromide.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60ml/min per

1.73m² body surface area as well as in cases where Spiromide is taken in combination with certain other drugs which may lead to an increase in potassium levels.

For some patients with metastatic castration-resistant prostate cancer, tumor progression has been observed during spironolactone treatment. Spironolactone binds to the androgen receptor and can increase the prostate-specific antigen (PSA) value.

In patients who are at high risk for radiocontrast nephropathy, furosemide is not recommended to be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with risperidone

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed.

Nevertheless, caution should be exercised and the risks and benefits of this combination or co- treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia.

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

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

DRUG INTERACTIONS

Absorption of spironolactone is increased if Furosemide and Spironolactone is taken together with food. The clinical relevance of this interaction is unknown.

The dosage of concurrently administered cardiac glycosides, diuretics, anti- hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with Furosemide and Spironolactone combination. A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors or angiotensin II receptor antagonists are added to furosemide therapy, or their dose level increased. The dose of Furosemide and Spironolactone combination should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or angiotensin II receptor antagonist or increasing their dose.

When combination of Furosemide and Spironolactone is taken in combination with potassium salts, with drugs which reduce potassium excretion, with non-steroidal anti-inflammatory drugs or with ACE inhibitors, an increase in serum potassium concentration and hyperkalaemia may occur.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.

Combination of Furosemide and Spironolactone and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with combination of Furosemide and

Spironolactone, resulting in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Levothyroxine: High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

Certain non-steroidal anti-inflammatory agents (e.g. indomethacin, acetylsalicylic acid) may attenuate the action of Furosemide and Spironolactone and may cause acute renal failure in cases of pre-existing hypovolemia or dehydration.

Salicylic toxicity may be increased by Furosemide and Spironolactone combination. Furosemide and Spironolactone may sometimes attenuate the effects of other drugs (e.g. the effects of antidiabetics and pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).

Furosemide and Spironolactone combination may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with Furosemide and Spironolactone combination if there are compelling medical reasons.

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Spironolactone may cause raised digoxin levels. Some electrolyte disturbances (e.g. Hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

Attenuation of the effect of Furosemide and Spironolactone combination may occur following concurrent administration of phenytoin.

Concomitant administration of carbamazepine or aminogluthimide may

increase the risk of hyponatremia.

Corticosteroids administered concurrently may cause sodium retention.

Both spironolactone and carbenoxolone may impair the action of the other substance. In this regard, liquorice in larger amounts acts in a similar manner to carbenoxolone. Corticosteroids, carbenoxolone, liquorice, B2 sympathomimetics in large amounts, and prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing Hypokalaemia.

Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of Furosemide and Spironolactone combination. Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

Cholestyramine: Hyperkalaemia could occur in the context of hyperchloremic metabolic acidosis in patients given Furosemide and Spironolactone combination concurrently with cholestyramine.

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

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 feminization of the genitalia in male offspring. Anti-androgenic effects have been reported in humans with the risk of ambiguous external genitalia in male newborns.

Furosemide and Spironolactone combination 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 Furosemide and Spironolactone combination 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

Adverse effects have been ranked under headings of frequency using the following convention: 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 ($< 1/10,000$); frequency not known (cannot be estimated from the available data).

Furosemide is generally well tolerated.

Blood and lymphatic system disorders

Frequency not known: 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 anemia or haemolytic anemia may develop. Eosinophilia is rare.

Nervous system disorders

Frequency not known:

Paraesthesia may occur.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.

Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension), headache.

Renal and urinary disorders Frequency not known:

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

Frequency not known:

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly.

Frequency uncommon:

Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.

Vascular disorders Frequency not known:

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 Frequency not known:

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

Skin and subcutaneous tissue disorders Frequency not known:

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), lichenoid reactions.

Metabolism and nutrition disorders

Frequency not known:

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 hypovolemia and dehydration, especially in elderly patients. Dizziness or leg cramps in the context of hypovolemia, 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 hemoconcentration 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 Frequency not known:

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

Exacerbation or activation of systemic lupus erythematosus. Gastro-intestinal disorders

Frequency not known:

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 Frequency not known:

Because of its chemical similarity to the sex hormones, spironolactone may make the nipples more sensitive to touch. Dose dependent mastodynia and

reversible gynecomastia 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 be impaired. Progression of castration-resistant prostate cancer.

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 Frequency not known:

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 Furosemide and Spironolactone combination 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.

Healthcare professionals are asked to report any suspected adverse reactions via the national pharmacovigilance reporting system.

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. hypovolemia, dehydration, hemoconcentration, 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

Pharmacotherapeutic group: Diuretics; High-ceiling diuretics and potassium-sparing agents.

ATC code: C03EB01

5.1 Pharmacodynamic properties

Furosemide: Furosemide is a diuretic acting on the Loop of Henle.

Spironolactone: Spironolactone is a competitive inhibitor of aldosterone.

Furosemide:

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and a hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis and the renin- angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

Spironolactone:

Spironolactone 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).

Spironolactone 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 spironolactone is based on water and salt depletion.

5.2 Pharmacokinetic properties

Furosemide: Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed from the gastrointestinal tract (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Bioavailability is about 65%. It has a biphasic half-life in plasma with a terminal elimination phase up to about 2 hours but this is prolonged in neonates, and in patients with hepatic and renal insufficiency. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is bound to plasma albumin and little biotransformation takes place. 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.

It is mainly excreted in the urine largely unchanged, but also in the form of glucuronide and free amine metabolites. Variable amounts are also excreted in the bile. Furosemide crosses the placental barrier and is excreted in milk. Non renal elimination is considerably increased in renal failure. The clearance of furosemide is not increased by haemodialysis.

In renal/ hepatic impairment

Where liver disease is present, biliary elimination is reduced up to 50%. Renal impairment has little effect on the elimination rate of furosemide, but less than 20% residual renal function increases the elimination time.

The elderly

The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present. Newborn A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

Spironolactone: Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulfur containing

metabolites (80%) and partly canrenone (20%). Although the plasma half-life of spironolactone itself is short (1.3 hours) the half-lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours). Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration ($t_{\max}$), peak plasma concentration ($C_{\max}$), and elimination half-life ($t_{1/2}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7- α -(thiomethyl) spironolactone 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.

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

Furosemide

Not relevant.

Spironolactone

Spironolactone 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.

Nonclinical data reveal no evidence of teratogenicity, but embryo-fetal toxicity has been seen in rabbits, and an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development. Endocrine disrupting effects have also been observed in female rodents at clinically relevant exposures. In adult rats, spironolactone was found to increase the length of the estrous cycle, and in female offspring exposed late in pregnancy, endocrine dysfunction persisting to adulthood was observed. In mice spironolactone inhibited ovulation and implantation, thereby decreasing fertility. The clinical relevance of these findings is unknown.

6. Pharmaceutical Particulars

6.1 List of Excipients

Corn starch, lactose, polyvinylpyrrolidone K-30, magnesium stearate-325, opadry white, and red iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

(To be confirmed)

6.4 Special Precautions for Storage

Protect from sunlight, moisture and heat.

Store below 30°C.

Keep all medicines out of sight & reach of children.

6.5 Nature and Content of container

Boxes of 20 tablets (2 x 10's blister Strips).

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing Authorization Holder

The Searle Company Limited,

F-319, S.I.T.E., Karachi, Pakistan.

8. Marketing Authorization Number

H2005/064

9. Date of first authorization/renewal of the authorization

To be confirmed.

10. Date of revision of the text