SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lasilactone 20mg/50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20mg Furosemide and 50mg Spironolactone.

Also contains 95mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

Hard capsules with a white opaque body and a blue opaque cap

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lasilactone 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 Lasilactone 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 Lasilactone 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

For oral administration.

Adults: 1-4 capsules daily.

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

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

The capsules should be swallowed whole. They 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 hypovolaemia or dehydration (with or without accompanying hypotension). Patients with an impaired renal function and a creatinine clearance below 30ml/min per 1.73 m^2 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 hyponatraemia, Addison's disease, during pregnancy and breast feeding women.

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

4.4 Special warnings and precautions for use

Spironolactone may cause vocal changes. In determining whether to initiate treatment with Lasilactone, 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 hypovolaemia 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 hypoproteinaemia, 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 Lasilactone 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. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Lasilactone.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60ml/min per 1.73m^2 body surface area as well as in cases where Lasilactone is taken in combination with certain other drugs which may lead to an increase in potassium levels.

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.

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 (see section 4.3).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Absorption of spironolactone is increased if Lasilactone 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 Lasilactone. 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 Lasilactone 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 Lasilactone 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.

Lasilactone 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 Lasilactone, 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. See section 4.4 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.indometacin, acetylsalicylic acid) may attenuate the action of Lasilactone and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.

Salicylic toxicity may be increased by Lasilactone. Lasilactone 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).

Lasilactone may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with Lasilactone 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 Lasilactone may occur following concurrent administration of phenytoin.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Corticosteroids administered concurrently may cause sodium retention.

Both spironolactone and carbenoloxone 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, B_2 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 Lasilactone. 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.

Colestyramine: Hyperkalaemia could occur in the context of hyperchloraemic metabolic acidosis in patients given Lasilactone concurrently with colestyramine.

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 Fertility, 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).

Lasilactone 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 Lasilactone must therefore not be used in breast-feeding mothers. See section 4.3.

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 (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥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 anaemia or haemolytic anaemia may develop. Eosinophilia is rare.

Nervous system disorders
Frequency not known:
Paraesthesiae may occur.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).

Dizziness, fainting and loss of consciousness.

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, hypoproteinaemia (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).

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 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
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 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
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 Lasilactone 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

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: Diuretics; High-ceiling diuretics and potassium-sparing agents, ATC code: C03EB01

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

Spironolactone: Spironolactone is a competitive inhibitor of aldosterone.

5.2 Pharmacokinetic properties

Furosemide: Furosemide is a short-acting diuretic; diuresis usually commences within one hour and lasts for four to six hours.

Spironolactone: Spironolactone, a competitive inhibitor of aldosterone, increases sodium excretion whilst reducing potassium loss at the distal renal

tubule. It has a slow and prolonged action, maximum response being usually attained after 2-3 days' treatment.

5.3 Preclinical safety data

Carinogenicity: Spironolactone has been shown to produce tumours 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 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

Capsule contents:
Microcrystalline cellulose
Lactose monohydrate
Talc
Magnesium stearate
Sodium starch glycolate type C

Capsule shell:
Indigotin (E132, FD&C Blue 2)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Keep the blister strip in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/Aluminium blister packs containing 28 or 50 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

Or trading as:

Sanofi-aventis or Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

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