Type A amendment compiled but not submitted: 24 October 2018

1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

SERVATRIN (tablet)

COMPOSITION

Each tablet of SERVATRIN contains:

Hydrochlorothiazide	25,0 mg
Timolol maleate	10,0 mg
Amiloride hydrochloride	2,5 mg

Excipients:

Dye Lennon lake blue (C.I. 73015), dye Lennon blue (C.I. 42090), lactose monohydrate, magnesium stearate, microcrystalline cellulose, purified talc, starch maize

Contains sugar: Lactose monohydrate 101,393 mg

CATEGORY AND CLASS

A 7.1.3 Other Hypotensives

PHARMACOLOGICAL ACTION

SERVATRIN is an antihypertensive combining timolol maleate, amiloride hydrochloride and hydrochlorothiazide, agents with complementary antihypertensive properties. Timolol maleate is

Mondia 26/10/2018

a beta-adrenergic blocking agent, amiloride hydrochloride is a potassium-sparing diuretic, and hydrochlorothiazide is a thiazide diuretic.

INDICATIONS

SERVATRIN is indicated for the treatment of hypertension.

CONTRAINDICATIONS

Hypersensitivity to the active ingredients.

SERVATRIN should not be given to patients with partial heart block, and should never be given to patients with phaeochromocytoma without concomitant alpha-adrenoceptor blocking therapy. It should not be given together with verapamil and neither drug should be administered within several days of discontinuing the other.

SERVATRIN is contraindicated in patients with bronchial asthma, bronchitis, bronchospasm or chronic respiratory diseases, metabolic acidosis, atrioventricular block, marked bradycardia (less than 50 per minute), heart failure refractory to digitalis, uraemia, hypoglycaemia, second and third degree heart block, peripheral vascular diseases and Raynaud's phenomenon.

SERVATRIN is contraindicated in pregnancy and lactation.

SERVATRIN should not be used in elderly patients, or in patients suffering from renal dysfunction without reducing the normal dose of SERVATRIN.

It is contraindicated in patients with metabolic acidosis (e.g. in diabetes) and after prolonged fasting.

In the peri-operative period, it is generally unwise to reduce the dosage to that which the patient is accustomed, as there may be danger of aggravation of angina pectoris or of hypertension. A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

SERVATRIN should not be given to patients with severe renal and/or hepatic insufficiency.

Potassium supplements are contraindicated in patients receiving SERVATRIN.

SERVATRIN should be used with caution in patients with impaired hepatic or renal function, or adrenal disease.

SERVATRIN is not recommended for the paediatric age group.

WARNINGS

SERVATRIN should be given to patient with congestive heart failure only when they are fully digitalised, and then only with great caution. Great care should be exercised in giving SERVATRIN to patients undergoing anaesthesia and myocardial depressants such as chloroform or either must be avoided.

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DOSAGE AND DIRECTIONS FOR USE

One to two tablets to be taken once a day.

Patients should be warned not to discontinue medicine except on the advice of their medical doctor and the importance of compliance with therapy should be stressed. Patients should be advised not to take other medicines without professional advice.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

The most common side effects to be expected are asthenia, fatigue and bradycardia. The side effects for the individual components are listed below.

Timolol maleate:

The most common side effects are nausea, vomiting, diarrhoea, fatigue and dizziness. Central nervous system effects include depression, malaise, hallucinations, vivid dreams and nightmares, disturbances of sleep and vision and overt psychosis. Bronchospasm may occur, particularly in patients suffering from asthma, bronchitis and other pulmonary diseases. Blood disorders and skin rashes may also occur. Other side effects reported include constipation, fluid retention and mass gain, muscle cramps, and dry mouth.

SERVATRIN should not be given to patients with bronchial asthma or bronchospasm, hypoglycaemia, metabolic acidosis, sinus bradycardia or partial heart block.

In congestive heart failure, SERVATRIN should only be administered when the patient is fully digitalised and then only with great caution.

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In diabetes mellitus SERVATRIN may reduce blood-sugar levels and may enhance the effects of hypoglycaemic agents. The signs of hypoglycaemia may be masked.

Cardiovascular effects include bradycardia, congestive heart failure, heart block, hypotension, cold extremities and paraesthesia.

Exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed, arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastrointestinal disturbances may also occur. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Safety during long-term administration has not been demonstrated.

Adverse reactions are more common in patients with renal decompensation and in patients who receive the drug intravenously.

SERVATRIN may mask the symptoms of hyperthyroidism although it does not interfere with thyroid-function tests.

It can be dangerous to administer SERVATRIN concomitantly with the following medicines: Hypoglycaemic agents, phenothiazines and various anti-arrhythmic agents.

PLEASE NOTE: Such drug interactions can have life-threatening consequences.

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Important:

Digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive heart failure is likely to develop. This combination can be considered despite the potentiation of negative chronotropic effects of the two medicines. Careful control of dosages and of the individual patient's response (and notably pulse rate) is essential in this situation.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

Administration to pregnant mothers shortly before giving birth, or during labour may result in the new-born infants being born hypotonic, collapsed and hypoglycaemic.

SERVATRIN should not be administered to patients with phaeochromocytoma without concurrent alpha-adrenergic blocking therapy.

INTERACTIONS

The effects of other myocardial depressant agents such as quinidine, procainamide or lignocaine may also be enhanced by SERVATRIN. The effects of SERVATRIN are diminished by beta-adrenergic stimulating agents, the hypotensive effects of SERVATRIN may be dangerously reversed and the peripheral vasoconstrictor effects enhanced by alpha-adrenergic stimulating agents such as nor-adrenaline or those with mixed alpha- and beta-adrenergic

stimulating properties such as adrenaline. Bradycardia may also occur.

The effects of SERVATRIN may be enhanced by adrenergic neurone blocking agents such as guanethidine, bethanidine, or reserpine, and the hypotensive effects by diuretics.

SERVATRIN may enhance some of the cardiac effects of digitalis and diminish others.

Cautions should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines which may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha-receptor stimulation may potentiate this effect.

If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker as severe rebound hypertension may occur.

Hydrochlorothiazide and Amiloride Hydrochloride:

Side-effects which may occur include allergies, skin rashes, pruritus, thirst, epigastric pain, anorexia, gastric irritation, nausea, vomiting, diarrhoea, constipation, photosensitivity, dizziness, headache, muscle spasm, weakness, inflammation of the salivary gland, loss of libido, and paraesthesias. Acute pancreatitis has been reported. Adverse effects such as pneumonitis, jaundice, and blood disorders including agranulocytosis, aplastic anaemia, thrombocytopenia, and leucopenia have occurred. Postural hypotension which may be accentuated by alcohol, antihypertensives, barbiturates, or narcotics has occurred. Hyper-parathyroidism has been

associated with thiazide diuretic therapy, and changes in serum lipids have been noted.

Minor psychiatric or visual changes have been reported (due to amiloride hydrochloride). Orthostatic hypotension and rises in blood urea-nitrogen concentration have been reported (due to amiloride hydrochloride). Occasional abnormalities in liver function tests have been reported (due to amiloride hydrochloride). Amiloride hydrochloride's potassium-sparing effect may lead to hyperkalaemia.

Potassium supplements should not be used with amiloride. In patients with impaired renal function, it may result is the rapid development of hyperkalaemia. It should be given with care to patients likely to develop acidosis, to patients with diabetes mellitus, and to those with impaired hepatic or renal function. Borderline renal and/or hepatic insufficiency may be unpredictably aggravated.

Necrotizing vasculitis, Stevens-Johnson syndrome (erythema multiforme) and purpura have been reported.

Hydrochlororthiazide may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. It may cause hyperuricaemia and precipitate attacks of gout in some patients. Electrolyte imbalances, hypochloraemic alkalosis, hypo-natraemia and hypokalaemia may occur. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and administration of digitalis or its glycosides may have to be temporarily suspended. Hypomagnesaemia has also occurred. The urinary excretion of calcium is reduced.

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Hyponatraemia may occur in patients with severe congestive heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet.

All patients should be carefully observed for signs of fluid or electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

Hydrochlorothiazide may enhance the toxicity of digitalis glycosides by depleting serum-potassium concentrations. Hydrochlorothiazide may diminish the response to pressor amines, such as noradrenaline.

Hydrochlorothiazide should be used with caution in patients with impaired hepatic or renal function, or with diabetes mellitus or adrenal disease. It may enhance the neuromuscular blocking action of non-depolarising muscle relaxants, such as tubo-curarine. It may enhance the effect of antihypertensive agents such as guanethidine, methyldopa, and rauwolfia alkaloids.

The potassium-depleting effect of hydrochlorothiazide may be enhanced by corticosteroids, corticotrophin, or carbenoxolone. Concomitant administration of hydrochlorothiazide and lithium is generally not recommended since the association may lead to toxic blood concentrations of lithium.

Blood-glucose concentrations should be monitored in patients taking antidiabetic agents, since requirements may change. Hydrochlorothiazide may interfere with a number of diagnostic tests, including tests for parathyroid function, serum concentrations of protein bound-iodine may increase without signs of thyroid disturbance. The product should be discontinued before

glucose tolerance tests are given to patients with diabetes mellitus. Serum electrolytes and blood-urea nitrogen should be estimated periodically.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals. Bradycardia associated with severe hypotension should be treated with intravenous atropine; if necessary, this should be followed up by a slow intravenous infusion of isoprenaline. Bronchospasm should be treated by intravenous aminophylline, and heart failure with digitalis and diuretics.

IDENTIFICATION

A light blue faintly mottled, flat, round tablet with bevelled edges, bisected on the one side and plain on the other side.

PRESENTATION

250 tablets packed in a white polypropylene securitainer sealed with a white low density polyethylene cap with tamper evident seal, together with a white foam insert and leaflet.

30 tablets are packed in a clear polyvinyl chloride film sealed with an aluminium foil backing. The blisters strips are packed into cardboard cartons together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25°C in a dry place.

Keep in original packaging until required for use.

Type A amendment compiled but not submitted: 24 October 2018

Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

V/7.1.3/354

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 10 March 1989

The date of the most recent amendment to the professional information as approved by the Authority: 10 March 1989

Botswana: B9316340 S2

Namibia: NS2 04/7.1.3/0172