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SCHEDULING STATUS:

Schedule 5

PROPRIETARY NAME (and dosage form):

SERENACE® 5 mg/ml Injection

SERENACE® 20 mg/2 ml Injection

COMPOSITION:

SERENACE 5 mg/ml Injection contains 5 mg haloperidol BP per ml

SERENACE 20 mg/2 ml Injection contains 10 mg haloperidol BP per ml

Serenace injection contains the following inactive ingredients: Lactic acid and sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Central nervous system depressants - Miscellaneous structures

PHARMACOLOGICAL ACTION:

It is postulated that the behavioural effect of neuroleptic drugs is mediated through the inhibitory pathways of the extrapyramidal midbrain system.

It is thought that haloperidol, a butyprophenone, may act by mimicking GABA (gamma aminobutyric acid) and opposing the action of glutamic acid, particularly in specific areas of the extrapyramidal system.

The anti-psychotic action of haloperidol could be correlated with surface tension lowering properties and the consequent ability to form a monomolecular film on certain cell membranes. Such a mechanism could contribute towards the action of haloperidol on GABA/glutamic acid transmitter systems and also on catecholamine transmitter systems.

Haloperidol blocks dopamine receptors, possibly by a feed-back mechanism that increases dopamine turnover in the brain.

INDICATIONS:

- Acute and chronic schizophrenia
- Mania and hypomania
- Organic psychoses
- Agitation in psychotic illness

Childhood behavioural disorders:

- Explosive hyperexcitability and extreme hyperactivity in children (i.e. aggressivity, mood lability, difficulty sustaining attention and poor frustration tolerance). The use is recommended as a short term treatment and should be reserved for those patients that fail to respond to psychotherapy or medications other than neuroleptics.
- Motor tics and vocal utterances of Gilles de la Tourette's syndrome.

CONTRA-INDICATIONS:

SERENACE should not be used in patients with Parkinson's disease, in severe toxic central nervous system depression, comatose states or in patients hypersensitive to SERENACE.
SERENACE is contra-indicated in patients with bone-marrow suppression, or phaeochromocytoma.
SERENACE should be used with caution or not at all in patients with impaired liver, kidney, cardiovascular, cerebrovascular, and respiratory function and in those with closed-angle glaucoma, parkinsonism, diabetes mellitus, hypothyroidism, myasthenia gravis, or prostatic hypertrophy.

WARNINGS:

Severe dystonic reactions have followed the use of SERENACE, particularly in children and

adolescents. It should therefore be used with extreme care in children.
SERENACE can potentiate the action of central nervous system depressants, including alcohol, general anaesthetics, hypnotics and sedatives and opioid anaesthetics.
SERENACE should be given with great caution in patients with arteriosclerosis who may have occult lesions of the basal ganglia.

Ambulatory patients should be warned that during the first few days of treatment SERENACE may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle.
Caution should be observed in the use of lithium salts together with high doses of SERENACE, as an encephalopathy syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis and elevated BUN, fasting blood sugar, and serum enzymes) has been observed and irreversible neurological toxicity and brain damage have followed the concomitant use of SERENACE and lithium. SERENACE should be discontinued in patients who experience early signs of this syndrome.

SERENACE has been associated with tardive dyskinesia, which may appear in some patients, especially the elderly, during long term therapy or after withdrawal of the medicine (see Side-effects). The syndrome is characterized by rhythmical involuntary movements of the tongue, puffing of cheeks, puckering of mouth, chewing movements, and sometimes, involuntary movements of the extremities. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome and, if the medication is stopped at that time, a more severe manifestation of the syndrome may be prevented.

High doses of SERENACE may potentiate the action of methyldopa.
Rare cases of sudden and unexpected death have been reported in association with the administration of SERENACE. Possible causes include cardiac arrhythmias or aspiration

and asphyxia due to suppression of cough and gag reflexes.

Abrupt withdrawal of SERENACE therapy is best avoided as mild symptoms resembling the withdrawal symptoms of dependence have been seen in patients receiving prolonged maintenance therapy.

INTERACTIONS:

The most common interactions encountered with SERENACE are adverse effects resulting from concomitant administration of agents with similar pharmacological actions.

- SERENACE should be administered cautiously to patients receiving anticoagulants, since interference with the effects of phenindione has been reported.
- Concurrent administration of carbamazepine has been reported to decrease serum SERENACE to very low levels. During chronic administration, SERENACE may elevate serum prolactin levels. The clinical significance of elevated serum prolactin levels is unknown. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer.
- When given with other agents that produce postural hypotension dosage adjustments may be necessary. However, it should be noted that SERENACE may reduce the antihypertensive action of guanethidine and other adrenergic neuron blockers.
- As SERENACE possesses antimuscarinic actions, it may potentiate the adverse effects of other antimuscarinics, including the antimuscarinic antiparkinsonian agents which may be given to treat phenothiazine-induced extrapyramidal effects.
- In theory, neuroleptics with dopamine-blocking activity and dopaminergic drugs such as those used to treat parkinsonism may be mutually antagonistic. Neuroleptics have been associated with the neuroleptic malignant syndrome, which is characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and coma.

Signs of autonomic dysfunction such as tachycardia, labile arterial pressure, and sweating may precede the onset of hyperthermia, acting as early warning signs.

- Concomitant administration of metoclopramide may increase the risk of neuroleptic-induced extrapyramidal effects and antiarrhythmics which prolong the QT-interval, may increase the likelihood of ventricular arrhythmias.
- Epinephrine should not be used since SERENACE may block its vasopressor activity and cause a further decrease in blood pressure.
- Care is required in epileptic patients receiving anticonvulsant therapy as SERENACE may lower the seizure threshold. SERENACE should be avoided if possible in untreated epileptics.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Dosage should be titrated to clinical efficacy, then reduced to the lowest effective level. Safety and prolonged administration of high dosages has not been demonstrated by controlled clinical trials. Children and debilitated or geriatric patients may be more sensitive to SERENACE and require adjustment of the starting dose. The maximum dose and maintenance doses are generally lower for these patients.

Adults

For the control of acute psychotic conditions, SERENACE may be given intramuscularly in doses of 2 to 10 mg; subsequent doses may be given hourly until symptoms are controlled although dosage intervals of 4 to 8 hours may be adequate. Up to 30 mg intramuscularly may be required for emergency control of very severely disturbed patients. The intravenous route may be used if required.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The table below contains adverse events categorized as follows utilizing the incidence rates: Very common ≥ 1/10 (≥ 10%); Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%); Uncommon ≥ 1/1000 and < 1/100 (≥ 0,1% and < 1%), Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01% and < 0,1%); Very rare < 1/10 000 (< 0,01%).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	*Uncommon*	Potentially fatal agranulocytosis
	Rare	Haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura
Metabolism and nutrition disorders	*Uncommon*	Anorexia, hyponatremia
	Rare	Hyperglycaemia, hypoglycaemia
Psychiatric disorders	*Uncommon*	Insomnia, agitation
	Rare	Restlessness, anxiety, delirium, catatonic-like states, depression
Nervous system disorders	*Common*	Neurological effects, especially extrapyramidal syndromes, are the most common. Where high dosage treatment is used, extrapyramidal side-effects may be encountered at an early stage in the form of dystonic reactions or motor restlessness (akathisia); neuroleptic malignant syndrome
	Uncommon	Convulsions
Eye disorders	*Rare*	Prolonged therapy may lead to deposition of pigment in the eyes; corneal and lens opacities have been observed; blurred vision; mydriasis, miosis
Cardiac disorders	*Uncommon*	Tachycardia, cardiac arrhythmias
Vascular disorders	*Common*	Hypotension
	Uncommon	Hypertension
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Laryngospasm, bronchospasm
	Rare	Increased depth of respiration, nasal congestion
Gastrointestinal disorders	*Common*	Hypersalivation
	Uncommon	Nausea, vomiting

	Rare	Constipation, diarrhoea, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders	*Uncommon*	Urticaria, exfoliative dermatitis, isolated cases of photosensitivity; diaphoresis
	Rare	Prolonged therapy may lead to deposition of pigment in the skin; erythema multiforme; contact sensitivity; maculopapular and acneiform skin reactions; loss of hair; a syndrome resembling systemic lupus erythematosus has been reported
Renal and urinary disorders	*Rare*	Urinary retention
Reproductive system and breast disorders	*Uncommon*	Gynaecomastia, galactorrhoea, increased libido
	Rare	Lactation, breast engorgement, mastalgia, menstrual irregularities, amenorrhoea, impotence, inhibition of ejaculation, priapism
General disorders and administration site conditions	*Uncommon*	Some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal.
Investigations	*Rare*	Weight gain; ECG changes, particularly Q and T- wave abnormalities; EEG changes; minor abnormalities of liver function tests

Special precautions:

A pseudo-parkinsonian rigidity syndrome may occur during the course of treatment which may also be treated with anti-parkinsonian agents. If symptoms and/or signs of parkinsonism manifest themselves, the dose of SERENACE should be reduced or treatment may be combined with an anti-parkinsonian agent.

Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis.

Care should be exercised in patients with severe cardiovascular disorders because of the possibility of transient hypotension. Epinephrine should not be used since SERENACE may block its vasopressor activity and cause a further decrease in blood pressure.

Care is required in epileptic patients receiving anticonvulsant therapy as SERENACE may

lower the seizure threshold. SERENACE should be avoided if possible in untreated epileptics.

Elderly and debilitated patients may be more prone to the adverse effects of SERENACE.

SERENACE effects on the vomiting centre may mask the symptoms of overdosage of other agents, or of disorders such as gastro-intestinal obstruction.

Administration at extremes of temperature may be hazardous since body temperature regulation is impaired by SERENACE.

Regular eye examinations are advisable for patients receiving long-term SERENACE therapy, and avoidance of undue exposure to direct sunlight is recommended.

Haematological parameters should also be monitored periodically.

Patients should remain supine for at least 30 minutes after parenteral administration of SERENACE; blood pressure should be monitored.

Abrupt withdrawal of SERENACE therapy is best avoided (see Warnings).

When SERENACE is used to control mania in cyclic disorders, a rapid mood swing to depression may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See Side-effects and Special precautions.

Treatment is symptomatic and supportive.

IDENTIFICATION:

SERENACE 5 mg/ml Injection: A clear, colourless solution

SERENACE 20 mg/2 ml Injection: A clear, colourless solution

PRESENTATION:

SERENACE 5 mg/ml Injection: Boxes containing 5 ampoules.

SERENACE 20 mg/2 ml Injection: Boxes containing 5 ampoules.

STORAGE INSTRUCTIONS:

Store in a dry place below 30 °C.

Protect from light.

Keep out of reach of children.

REGISTRATION/REFERENCE NUMBERS:

SERENACE 5 mg/ml Injection: B1541 (Act 101/1965)

SERENACE 20 mg/2 ml Injection: K/2.6.5/72

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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