Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Serenace 5 mg/ml Ampoule Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5 mg of haloperidol.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, sterile, aqueous solution with a pH of 3.0 - 3.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Psychotic disorders – schizophrenia, mania and hypomania, especially paranoid psychoses.

Mental or behavioural problems such as aggression, hyperactivity and self-mutilation in the mentally retarded.

Moderate to severe psychomotor agitation *eg* severe motor tics and Gilles de la Tourette Syndrome, excitement, and violent or dangerously impulsive behaviour.

Nausea, vomiting and intractable hiccup.

4.2 Posology and method of administration

There is considerable variation from patient to patient in the response to treatment and the dosage required. As with all antipsychotics, dosage should be individualised according to the needs and response of each patient.

To determine the initial dosage, consideration should be given to the patient's age, severity of symptoms and previous response to other antipsychotic therapy. Oral dosage may be given in single or divided doses. Administration twice daily is sufficient in most cases.

Adults
Psychotic behaviour; mental or behavioural problems; moderate to severe psychomotor agitation or impulsive behaviour; mania and hypomania.

Initial Treatment
For the control of acutely agitated patients showing moderate symptoms an intramuscular injection of 2 – 10mg may be given. Depending on the response of the patient subsequent doses may be given every 4 – 8 hours up to a maximum of 18mg/day.

Infrequently, severely disturbed patients may require an initial dose of up to 18mg.

Maintenance treatment
Once a satisfactory therapeutic response has been achieved, dosage should be reduced gradually to the lowest effective maintenance level. If possible, maintenance treatment should be oral.

Bioequivalence from the oral route is about 60% of that from intramuscular injection, so readjustment of the dose may be required.

Nausea and vomiting
0.5 to 2mg I.M. daily

Elderly
Half the recommended adult starting dose may be sufficient for therapeutic response in the elderly. The maximum and maintenance dose will generally be lower for debilitated or geriatric patients who may be more sensitive to Serenace.

Children
Parenteral administration is not recommended for children.

Route of administration
By intramuscular or intravenous injection.

4.3 Contraindications

Comatose states, patients with Parkinson's disease or a sensitivity to haloperidol, and use during lactation. Patients with lesions of the basal ganglia.

- Clinically significant cardiac disorders (e.g. recent acute myocardial infraction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products).
- QTc interval prolongation.
- History of ventricular arrhythmia or Torsades de pointes.
- Uncorrected hypokalaemia.
- Other QT prolonging drugs.

4.4 Special warnings and precautions for use

Liver disease, renal failure, phaeochromocytoma, conditions predisposing to epilepsy (e.g.alcohol withdrawal or brain damamge). May be given to epileptics but usual anticonvulsant therapy could be continued.

Caution should be exercised in the case of patients with cardiovascular disease or family history of QT prolongation if considering introduction of haloperidol.
Baseline ECG should be performed prior to treatment (*see section 4.3, Contraindications*). During therapy, the need for ECG monitoring should be assessed on an individual patient basis.
Whilst on therapy, reduce dose if QT is prlonged and discontinue if QT_c is >500ms.
Periodic electrolyte monitoring is recommended.

Addition of other antipsychotic medication to haloperidol should be avoided.

Use cautiously in thyrotoxic patients and those with arteriosclerosis who may have occult or manifest lesions of the basal ganglia. Such patients may be more prone to develop extrapyramidal symptoms.

Administer with care to patients with severe cardiovascular disorders, because of the possibility of transient hypotension. Should hypotension occur and a vasopressor be required, adrenaline should not be used since haloperidol may block its vasopressor activity and further lowering of the blood pressre may occur.

Cases of sudden death have been reported in psychiatric patients receiving antipsychotic drugs, including haloperidol.

The risk benefit of haloperidol treatment should be fully asssessed before treatment is commenced and patients with risk factors for ventricular arrythmias such as cardiac disease; subarachnoid haemorrhage; metabolic abnormalities such as hypokalaemia, hypocalcaeimia, hypomagnesaemia; starvation; alcohol abuse or those receiving concomitant therapy with other drugs known to prolong the QT interval, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment, to obtain steady plasma levels.

Acute withdrawal symptoms including nausea, vomiting and insomnia have rarely been described after cessation of high doses of antipsychotic drugs. Recurrence of psychotic syptoms may also occur, and emergence of involutary movement disorders (such as akanthisia, dystonia and dyskinesia) have been reported.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

As with antipsychotic agents, haloperidol should not be used alone where depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist. Haloperidol may impair the metabolism of tricyclic antideprssants (clinical significance unknown).

If concomitant anti-Parkinson medication is required, it may have to be continued after haoperidol is discontinued to take account of any differences in excretion rates. The physician should keep in mind the possible anticholinergic effects associtated with anti-Parkinson agents. Prolonged use especially at high doses may result in tardive dyskinesia.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Serenace and preventative measures undertaken.

Increased mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There is insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Serenace is not licenced for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Haloperidol may potentiate the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics. Enhanced CNS effects (sedation, mental disturbances) have been reported with the combined use of methyldopa and haloperidol.

In rare cases, an encephalopathy-like syndrome has been reported in combination with lithium and Haloperidol. It remains controversial whether these cases represent a distinct clinical entity or whether they are in fact cases of NMS and/or lithium toxicity. Signs of encephalopathy-like syndrome include confusion, disorientation, headache, and disturbances of balance and drowsiness. One report showing symptomless EEG abnormalities on the combination has suggested that EEG monitoring might be advisable.

When lithium and Haloperidol therapy are used concomitantly, Haloperidol should be given in the lowest effective dose and lithium levels should be monitored and kept below 1mmol/L. If symptoms of encephalopathy-like syndrome occur, therapy should be stopped immediately.

Haloperidol when co-administered with indometacin may lead to severe drowsiness and confusion.

Increased levels of Haloperidol have been reported during concomitant administration of quinidine, buspirone and

fluoxetine, Haloperidol plasma levels should therefore be monitored and reduced if necessary.

Haloperidol may impair the metabolism of tricyclic antidepressants and the anti-Parkinson effects of levodopa. Serenace may antagonise the action of adrenaline and other sympathomimetic agents.

Possible interactions have been reported between Haloperidol and Carbamazepine. Haloperidol levels have been shown to be reduced by approximately 50% when Carbamazepine is administered concurrently.

The psychotic symptoms in some patients have been exacerbated in association with these lowered Haloperidol levels but in some instances increased efficacy was seen, possibly as a result of the central action of carbamazepine itself. The mechanism for this interaction is thought to be enzyme induction and increased hepatic metabolism of Haloperidol.

There is a potential risk of prolongation of the QT interval in patients receiving both haloperidol and other drugs with known QT prolonging properties. This risk may also occur with other drugs causing electrolyte disturbances or metabolic inhibitors of haloperidol.

4.6 Fertility, pregnancy and lactation

Pregnancy: The safety of haloperidol in pregnancy has not been established. Reproduction studies in rodents have shown an increased incidence of resorption, reduced fertility and pup mortality. No specific teratogenic effect has been reported in rats, rabbits or dogs but cleft palate and open eye syndrome have been reported in mice.

No well-controlled studies of Haloperidol use in pregnant women have been conducted.

Two cases of foetal limb malformation have been reported following maternal use of Haloperidol, combined with other drugs during the first trimester. No causal relationship has been established. Use of Haloperidol during pregnancy requires that the anticipated benefit be weighed against the possible hazards to mother and foetus.

Lactation: Haloperidol has been detected in breast milk. If use of Haloperidol is considered essential, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Haloperidol may impair alertness, especially at the start of treatment. These effects may be potentiated by alcohol. Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment, until their susceptibility is known.

4.8 Undesirable effects

Central Nervous System
Extrapyramidal symptoms such as Parkinson-like symptoms, akinesia, akathisia, dyskinesia, dystonia may develop during Haloperidol treatment, very rarely dystonia has been reported to produce laryngeal/pharyngeal spasm associated with gagging, respiratory distress and asphyxia.

In common with other antipsychotics Haloperidol has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose, or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high dose therapy. Characteristic symptoms are rhythmical involuntary movements of the tongue, face, mouth or jaw, sometimes accompanied by involuntary movements of the extremities. They may persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.

At the first signs of tardive dyskinesia, which may be orofacial dyskinesia the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. The appearance of fine vermicular movements of the tongue may be an early warning sign of tardive dyskinesia and the full syndrome may not develop if the medication is stopped at this stage. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal

persisting dyskinesia. Should it be necessary to reinstate treatment, the antipsychotic agent may mask the syndrome. Anti-Parkinsonian agents have proved of little value in this syndrome.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Some degree of sedation may occur, particularly with higher doses and at the start of treatment. The elderly appear more susceptible.

Other effects have been reported rarely: confusional states or epileptic fits, agitation, depression, insomnia, drowsiness, headache, vertigo and exacerbation of psychotic symptoms.

At low doses in susceptible (especially non-psychotic) individuals, Haloperidol may cause unpleasant subjective feelings of being mentally dulled or slowed down, dizziness, headache or paradoxical effects of excitement, agitation or insomnia.

In common with other antipsychotics Haloperidol has been associated with rare cases of neuroleptic malignant syndrome, an idiosyncratic response 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. Recovery usually occurs within five to seven days of antipsychotic withdrawal. Affected patients should be carefully monitored.

Other effects have been reported rarely: confusional states or epileptic fits, depression, drowsiness, vertigo and exacerbation of psychotic symptoms.

Gastro-intestinal System: Gastro-intestinal symptoms including nausea, loss of appetite, constipation and dyspepsia have been reported.

Endocrinological System: In common with other antipsychotics, hormonal effects include hyperprolactinaemia which could cause galactorrhoea, gynaecomastia and oligo – or amenorrhoea. Impairment of sexual function, including erection dysfunction, priapism and ejaculation have been reported.

Cardiovascular System: Tachycardia and dose-related hypotension is uncommon, but can occur, particularly in the elderly or after parenteral administration. Hypertension has also been reported.

There is a potential risk of QT prolongation with haloperidol, which may rarely result in precipitation of ventricular arrhythmias such as ventricular tachycardia or fibrillation, torsades de pointes, cardiac arrest or sudden unexplained death. This may occur more frequently with high doses, intravenous administration and in predisposed patients (see Precautions and Warnings).

Autonomic Nervous System: Autonomic effects such as blurring of vision, dry mouth, excessive salivation, urinary retention and hyperhidrosis have been reported.

Dermatological System: Oedema and skin reactions including exfoliative dermatitis, erythema multiforme and photosensitisation, are rarely reported.

Other adverse reactions: The following effects have been reported rarely: Cholestatic hepatitis, jaundice, transient abnormalities of liver function tests may occur in the absence of jaundice.

Impairment of body temperature could occur at high doses. Abrupt discontinuation of high doses of antipsychotics has very rarely resulted in acute withdrawal symptoms, including nausea, vomiting and insomnia. Gradual withdrawal is advisable.

Very rarely the following have also been reported: blood dyscrasias, including agranulocytosis, thrombocytopenia and transient leucopenia; hypersensitivity reactions including anaphylaxis have been reported.

Rare cases of sudden and unexplained death have been reported in psychiatric patients receiving treatment with antipsychotics including Haloperidol. The nature of the evidence makes it impossible to determine the contributory role, if any, of the drug.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

4.9 Overdose

Intensification of the known pharmacological and adverse effects may occur. The most prominent would be severe extrapyramidal symptoms, hypotension or sedation. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. Extrapyramidal reactions may include muscular weakness or rigidity and a generalised or localised tremor. With accidental overdosage hypothermia, bradycardia, sinus arrhythmia and hypertension have been reported in young children.

No specific antidote has been identified.

In the event of overdosage the stomach should be emptied by aspiration and lavage. Emetics should not be used. Establishment of patient airway and artificial ventilation may be needed. Hypotension may be counteracted by placing the patient in the head-down position and by the use of a plasma expander and careful use of a vasopressor agent such as noradrenaline. Adrenaline should not be used. Severe extrapyramidal reactions should be treated with parenteral antihistamines or antiparkinsonian drugs. The relatively long plasma elimination half-life of haloperidol should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antipsychotic N05A

Haloperidol is a butyrophenone. Its pharmacological profile of activity includes a pronounced capacity to induce extrapyramidal reactions and a low incidence of autonomic side effects, such as hypotension.

5.2 Pharmacokinetic properties

The pharmacokinetics of Haloperidol has been studied in healthy volunteers and patients. In volunteers, following a single intravenous or oral dose, serum elimination half-life ranged from 10-19 hours and 12-38 hours respectively. Similar elimination half lives where observed in patients after administration of a single oral or intramuscular dose of the drug or after withdrawal of the drug from patients who were in a steady state. Steady state serum levels were usually achieved within 6 days of a fixed oral dosage.

A butyrophenone variably absorbed from the gastrointestinal tract but with extensive first pass metabolism in the liver with entero hepatic recycling. The drug is widely distributed in the body and is strongly protein bound.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Keep ampoule in the outer carton.

6.5 Nature and contents of container

Clear, neutral glass ampoules, with a yellow band around the neck constriction, containing 1 ml of solution.

Pack sizes
Ampoules come in pack sizes of 6 or 10, which are packed into cardboard cartons.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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