Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Serenace 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains haloperidol 10 mg.

Excipients: Each tablet contains 190mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Pale pink biconvex tablet coded 'NORTON 10' on one face, 'SERENACE' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

4.1 Therapeutic Indications

Adult patients aged 18 years and above

- Treatment of schizophrenia and schizoaffective disorder.
- Acute treatment of delirium when non-pharmacological treatments have failed.
- Treatment of moderate to severe manic episodes associated with bipolar I disorder.
- Treatment of acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder.
- Treatment of persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non pharmacological treatments have failed and when there is a risk of harm to self or others.
- Treatment of tic disorders, including Tourette's syndrome, in patients with severe impairment after educational, psychological and other pharmacological treatments have failed.
- Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated.

Paediatric patients

Treatment of:

- Schizophrenia in adolescents aged 13 to 17 years when other pharmacological treatments have failed or are not tolerated.
- Persistent, severe aggression in children and adolescents aged 6 to 17 years with autism or pervasive developmental disorders, when other treatments have failed or are not tolerated.
- Tic disorders, including Tourette's syndrome, in children and adolescents aged 10 to 17 years with severe impairment after educational, psychological and other pharmacological treatments have failed.

4.2 Posology and method of administration

Posology

Adults
A low initial dose is recommended, which subsequently may be adjusted according to the patient's response. Patients must always be maintained on the minimal effective dose (see section 5.2).

The dose recommendations for Serenace tablets are presented in Table 1.

Table 1: Haloperidol dose recommendations for adults aged 18 years and above

Treatment of schizophrenia and schizoaffective disorder • 2 to 10 mg/day orally, as a single dose or in 2 divided doses. Patients with first-episode schizophrenia generally respond to 2 to 4 mg/day, whereas patients with multiple-episode schizophrenia may need doses up to 10 mg /day. • Adjustments to the dose may be made every 1 to 7 days. • Doses above 10 mg/day have not demonstrated superior efficacy to lower doses in the majority of patients and may cause an increased incidence of extrapyramidal symptoms. The individual benefit-risk should be assessed when considering doses above 10 mg/day. • The maximum dose is 20 mg/day because safety concerns outweigh the clinical benefits of treatment at higher doses.
Acute treatment of delirium when non-pharmacological treatments have failed • 1 to 10 mg/day orally, as a single dose or in 2 to 3 divided doses. • Treatment should be started at the lowest possible dose, and the dose should be adjusted in increments at 2- to 4-hour intervals if agitation continues, up to a maximum of 10 mg/day.
Treatment of moderate to severe manic episodes associated with bipolar I disorder • 2 to 10 mg/day orally, as a single dose or in 2 divided doses. • Adjustments to the dose may be made every 1 to 3 days. • Doses above 10 mg/day have not demonstrated superior efficacy to lower doses in the majority of patients and may cause an increased incidence of extrapyramidal symptoms. The individual benefit-risk should be assessed when considering doses above 10 mg/day. • The maximum dose is 15 mg/day because safety concerns outweigh the clinical benefits of treatment at higher doses. • The continued use of Serenace should be evaluated early in treatment (see section 4.4).
Treatment of acute psychomotor agitation associated with psychotic disorder or manic episodes of bipolar I disorder • 5 to 10 mg orally, repeated after 12 hours if necessary to a maximum of 20 mg/day. • The continued use of Serenace should be evaluated early in treatment (see section 4.4). • When switching from haloperidol intramuscular injection, Serenace orally should be initiated at a 1:1 dose conversion rate followed by dose adjustment according to clinical response.
Treatment of persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others • 0.5 to 5 mg/day orally, as a single dose or in 2 divided doses. • Adjustments to the dose may be made every 1 to 3 days. • The need for continued treatment must be reassessed after no more than 6 weeks.

Treatment of tic disorders, including Tourette's syndrome, in patients with severe impairment after educational, psychological and other pharmacological treatments have failed • 0.5 to 5 mg/day orally, as a single dose or in 2 divided doses. • Adjustments to the dose may be made every 1 to 7 days. • The need for continued treatment must be reassessed every 6 to 12 months.
Treatment of mild to moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated • 2 to 10 mg/day orally, as a single dose or in 2 divided doses. • Adjustments to the dose may be made every 1 to 3 days.

Treatment withdrawal
Gradual withdrawal of haloperidol is advisable (see section 4.4).

Missed dose
If patients miss a dose, it is recommended that they take the next dose as usual, and do not take a double dose.

Special populations

Elderly
The following initial haloperidol doses are recommended in elderly patients:

- Treatment of persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others – 0.5 mg/day.
- All other indications – half the lowest adult dose.

The haloperidol dose may be adjusted according to the patient's response. Careful and gradual dose up-titration in elderly patients is recommended.

The maximum dose in elderly patients is 5 mg/day.

Doses above 5 mg/day should only be considered in patients who have tolerated higher doses and after reassessment of the patient's individual benefit-risk profile.

Renal impairment
The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. No dose adjustment is recommended, but caution is advised when treating patients with renal impairment. However, patients with severe renal impairment may require a lower initial dose, with subsequent adjustments at smaller increments and at longer intervals than in patients without renal impairment (see section 5.2).

Hepatic impairment
The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. Since haloperidol is extensively metabolised in the liver, it is recommended to halve the initial dose, and adjust the dose with smaller increments and at longer intervals than in patients without hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The dose recommendations for Serenace tablets are presented in Table 4.

Table 2: Haloperidol dose recommendations for paediatric population

Treatment of schizophrenia in adolescents aged 13 to 17 years when other pharmacological treatments have failed or are not tolerated • The recommended dose is 0.5 to 3 mg/day, administered orally in divided doses (2 to 3 times a day). • It is recommended to assess the individual benefit-risk when considering doses above 3 mg/day. • The maximum recommended dose is 5 mg/day. • The treatment duration must be individually evaluated.
Treatment of persistent, severe aggression in children and adolescents aged 6 to 17 years with autism or pervasive developmental disorders, when other treatments have failed or are not tolerated • The recommended doses are 0.5 to 3 mg/day in children aged 6 to 11 years and 0.5 to 5 mg/day in adolescents aged 12 to 17 years, administered orally in divided doses (2 to 3 times a day). • The need for continued treatment must be reassessed after 6 weeks.
Treatment of tic disorders, including Tourette's syndrome, in children and adolescents aged 10 to 17 years with severe impairment after educational, psychological and other pharmacological treatments have failed • The recommended doses are 0.5 to 3 mg/day in children and adolescents aged 10 to 17 years, administered orally in divided doses (2 to 3 times a day). • The need for continued treatment must be reassessed every 6 to 12 months.

The safety and efficacy of Serenace tablets in children below the ages defined in the indications have not been established. Data are not available for children aged less than 3 years.

Method of administration
Serenace tablets are for oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Comatose state
- Central nervous system (CNS) depression
- Parkinson's disease
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Known QTc interval prolongation or congenital long QT syndrome
- Recent acute myocardial infarction
- Uncompensated heart failure
- History of ventricular arrhythmia or torsades de pointes
- Uncorrected hypokalaemia
- Concomitant treatment with medicinal products that prolong the QT interval (see section 4.5).

4.4 Special warnings and precautions for use

Increased mortality in elderly people with dementia
Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotics, including haloperidol (see section 4.8.).

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in patients treated with antipsychotics was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that treatment of elderly patients with haloperidol is also associated with increased mortality. This association may be stronger for haloperidol than for atypical antipsychotic medicinal products, is most pronounced in the first 30 days after the start of treatment, and persists for at least 6 months. The extent to which this association is attributable to the medicinal product, as opposed to being confounded by patient characteristics, has not yet been elucidated.

Cardiovascular effects
QTc prolongation and/or ventricular arrhythmias, in addition to sudden death, have been reported with haloperidol (see sections 4.3 and 4.8). The risk of these events appears to increase with high doses, high plasma concentrations, in predisposed patients or with parenteral use, particularly intravenous administration.

Caution is advised in patients with bradycardia, cardiac disease, family history of QTc prolongation or history of heavy alcohol exposure. Caution is also required in patients with potentially high plasma concentrations (see section 4.4, Poor metabolisers of CYP2D6).

A baseline ECG is recommended before treatment. During therapy, the need for ECG monitoring for QTc interval prolongation and for ventricular arrhythmias must be assessed in all patients. Whilst on therapy, it is recommended to reduce the dose if QTc is prolonged, but haloperidol must be discontinued if the QTc exceeds 500 ms.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for ventricular arrhythmias and must be corrected before treatment with haloperidol is started. Therefore, baseline and periodic electrolyte monitoring is recommended.

Tachycardia and hypotension (including orthostatic hypotension) have also been reported (see section 4.8). Caution is recommended when haloperidol is administered to patients manifesting hypotension or orthostatic hypotension.

Cerebrovascular events
In randomised, placebo-controlled clinical studies in the dementia population, there was an approximately 3-fold increased risk of cerebrovascular adverse events with some atypical antipsychotics. Observational studies comparing the stroke rate in elderly patients exposed to any antipsychotic to the stroke rate in those not exposed to such medicinal products found an increased stroke rate among exposed patients. This increase may be higher with all butyrophenones, including haloperidol. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other patient populations. Haloperidol must be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome
Haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased serum creatine phosphokinase levels. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment must be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia
Tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of the medicinal product. The syndrome is mainly characterised by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients.

The syndrome may be masked when treatment is reinstituted, when the dose is increased or when a switch is made to a different antipsychotic. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including haloperidol, must be considered.

Extrapyramidal symptoms
Extrapyramidal symptoms may occur (e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia). The use of haloperidol has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Acute dystonia may occur during the first few days of treatment with haloperidol, but later onset as well as onset after dose increases has been reported. Dystonic symptoms can include, but are not limited to, torticollis, facial grimacing, trismus, tongue protrusion, and abnormal eye movements, including oculogyric crisis. Males and younger age groups are at higher risk of experiencing such reactions. Acute dystonia may necessitate stopping the medicinal product.Antiparkinson medicinal products of the anticholinergic type may be prescribed as required to manage extrapyramidal symptoms, but should not be prescribed routinely as a preventive measure. If concomitant treatment with an antiparkinson medicinal product is required, it may have to be continued after stopping haloperidol if its excretion is faster than that of haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The possible increase in intraocular pressure must be considered when anticholinergic medicinal products, including antiparkinson medicinal products, are administered concomitantly with haloperidol.

Seizures/Convulsions
It has been reported that seizures can be triggered by haloperidol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to seizures (e.g. alcohol withdrawal and brain damage).

Hepatobiliary concerns
As haloperidol is metabolised by the liver, dose adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 and 5.2). Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported (see section 4.8).

Endocrine system concerns
Thyroxin may facilitate haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism must be used only with caution and must always be accompanied by therapy to achieve a euthyroid state.

Hormonal effects of antipsychotics include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligomenorrhea or amenorrhoea (see section 4.8). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics and human breast tumours has been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Haloperidol must be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours (see section 5.3).

Hypoglycaemia and syndrome of inappropriate antidiuretic hormone secretion have been reported with haloperidol (see section 4.8).

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotics. 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 haloperidol and preventive measures undertaken.

Treatment response and withdrawal
In schizophrenia, the response to antipsychotic treatment may be delayed.

If antipsychotics are withdrawn, recurrence of symptoms related to the underlying condition may not become apparent for several weeks or months.

There have been very rare reports of acute withdrawal symptoms (including nausea, vomiting and insomnia) after abrupt withdrawal of high doses of antipsychotics. Gradual withdrawal is advisable as a precautionary measure.

Patients with depression
It is recommended that haloperidol is not used alone in patients in whom depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist (see section 4.5).

Switch from mania to depression
There is a risk in the treatment of manic episodes of bipolar disorder for patients to switch from mania to depression. Monitoring of patients for the switch to a depressive episode with the accompanying risks such as suicidal behaviour is important in order to intervene when such switches occur.

Poor metabolisers of CYP2D6
Haloperidol should be used with caution in patients who are known poor metabolisers of cytochrome P450 (CYP) 2D6 and who are coadministered a CYP3A4 inhibitor.

Paediatric population
Available safety data in the paediatric population indicate a risk of developing extrapyramidal symptoms, including tardive dyskinesia, and sedation. Limited long-term safety data are available.

Excipients
With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Cardiovascular effects

- Haloperidol is contraindicated in combination with medicinal products known to prolong the QTc interval (see section 4.3). Examples include:
- Class IA antiarrhythmics (e.g. disopyramide, quinidine).
- Class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol).
- Certain antidepressants (e.g. citalopram, escitalopram).
- Certain antibiotics (e.g. azithromycin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, telithromycin).
- Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antifungals (e.g. pentamidine).
- Certain antimalarials (e.g. halofantrine).
- Certain gastrointestinal medicinal products (e.g. dolasetron).
- Certain medicinal products used in cancer (e.g. toremifene, vandetanib).
- Certain other medicinal products (e.g. bepridil, methadone).

This list is not exhaustive.

Caution is advised when haloperidol is used in combination with medicinal products known to cause electrolyte imbalance (see section 4.4).

Medicinal products that may increase haloperidol plasma concentrations
Haloperidol is metabolised by several routes (see section 5.2). The major pathways are glucuronidation and ketone reduction. The cytochrome P450 enzyme system is also involved, particularly CYP3A4 and, to a lesser extent, CYP2D6. Inhibition of these routes of metabolism by another medicinal product or a decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. The effect of CYP3A4 inhibition and of decreased CYP2D6 enzyme activity may be additive (see section 5.2). Based on limited and sometimes conflicting information, the potential increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor is coadministered may range between 20 to 40%, although in some cases, increases of up to 100% have been reported.

Examples of medicinal products that may increase haloperidol plasma concentrations (based on clinical experience or drug interaction mechanism) include:

- CYP3A4 inhibitors – alprazolam, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, saquinavir, verapamil, voriconazole.
- CYP2D6 inhibitors – bupropion, chlorpromazine, duloxetine, paroxetine, promethazine, sertraline, venlafaxine.
- Combined CYP3A4 and CYP2D6 inhibitors: fluoxetine, ritonavir.
- Uncertain mechanism – buspirone.

This list is not exhaustive.

Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc-prolongation (see section 4.4). Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day).

It is recommended that patients who take haloperidol concomitantly with such medicinal products be monitored for signs or symptoms of increased or prolonged pharmacologic effects of haloperidol, and the haloperidol dose be decreased as deemed necessary.

Medicinal products that may decrease haloperidol plasma concentrations
Coadministration of haloperidol with potent enzyme inducers of CYP3A4 may gradually decrease the plasma concentrations of haloperidol to such an extent that efficacy may be reduced. Examples include:

- Carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort (*Hypericum perforatum*).

This list is not exhaustive.

Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen in about 2 weeks and may then be sustained for the same period of time after the cessation of therapy with the medicinal product. During combination treatment with inducers of CYP3A4, it is recommended that patients be monitored and the haloperidol dose increased as deemed necessary. After withdrawal of the CYP3A4 inducer, the concentration of haloperidol may gradually increase and therefore it may be necessary to reduce the haloperidol dose.

Sodium valproate is known to inhibit glucuronidation, but does not affect haloperidol plasma concentrations.

Effect of haloperidol on other medicinal products
Haloperidol can increase the CNS depression produced by alcohol or CNS-depressant medicinal products, including hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic medicinal products (e.g. stimulants like amphetamines) and reverse the blood pressure-lowering effects of adrenergic-blocking medicinal products such as guanethidine.

Haloperidol may antagonise the effect of levodopa and other dopamine agonists.

Haloperidol is an inhibitor of CYP2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants (e.g. imipramine, desipramine), thereby increasing plasma concentrations of these medicinal products.

Other forms of interaction
In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity.

Nonetheless, it is advised that in patients who are treated concomitantly with lithium and haloperidol, therapy must be stopped immediately if such symptoms occur.

Antagonism of the effect of the anticoagulant phenindione has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (more than 400 pregnancy outcomes) indicate no malformative or foeto/ neonatal toxicity of haloperidol. However, there have been isolated case reports of birth defects following foetal exposure to haloperidol, mostly in combination with other medicinal products. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of haloperidol during pregnancy.

Newborn infants exposed to antipsychotics (including haloperidol) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, it is recommended that newborn infants be monitored carefully.

Breastfeeding
Haloperidol is excreted in human milk. Small amounts of haloperidol have been detected in plasma and urine of breast-fed newborns of mothers treated with haloperidol. There is insufficient information on the effects of haloperidol in breast-fed infants. A decision must be made whether to discontinue breastfeeding or to discontinue haloperidol therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Haloperidol elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients (see section 4.4).

4.7 Effects on ability to drive and use machines

Haloperidol has a moderate influence on the ability to drive and use machines. Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. It is recommended that patients be advised not to drive or operate machines during treatment, until their susceptibility is known.

4.8 Undesirable effects

The safety of haloperidol was evaluated in 284 haloperidol-treated patients who participated in 3 placebo-controlled clinical studies and in 1295 haloperidol-treated patients who participated in 16 double-blind active comparator-controlled clinical studies.

Based on pooled safety data from these clinical studies, the most commonly reported adverse reactions were: extrapyramidal disorder (34%), insomnia (19%), agitation (15%), hyperkinesia (13%), headache (12%), psychotic disorder (9%), depression (8%), weight increased (8%), tremor (8%), hypertonia (7%), orthostatic hypotension (7%), dystonia (6%) and somnolence (5%).

In addition, the safety of haloperidol decanoate was evaluated in 410 patients who participated in 3 comparator studies (1 comparing haloperidol decanoate versus fluphenazine and 2 comparing the decanoate formulation to oral haloperidol), 9 open label studies and 1 dose response study.

Table 3 lists adverse reactions as follows:

- Reported in clinical studies with haloperidol.
- Reported in clinical studies with haloperidol decanoate and relate to the active moiety.
- From postmarketing experience with haloperidol and haloperidol decanoate.

Adverse reaction frequencies are based on (or estimated from) clinical trials or epidemiology studies with haloperidol, and classified using the following convention:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data.

The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 3: Adverse reactions

System Organ Class	**Adverse Reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders			Leukopenia		Pancytopenia Agranulocytosis Thrombocytopenia Neutropenia
Immune system disorders			Hypersensitivity		Anaphylactic reaction
Endocrine disorders				Hyperprolactinaemia	Inappropriate antidiuretic hormone secretion
Metabolic and nutritional disorders					Hypoglycaemia
Psychiatric disorders	Agitation Insomnia	Psychotic disorder Depression	Confusional state Loss of libido Libido decreased Restlessness		
Nervous system disorders	Extrapyramidal disorder Hyperkinesia Headache	Tardive dyskinesia Akathisia Bradykinesia Dyskinesia Dystonia Hypokinesia Hypertonia Dizziness Somnolence Tremor	Convulsion Parkinsonism Sedation Muscle contractions involuntary	Neuroleptic malignant syndrome Motor dysfunction Nystagmus	Akinesia Cogwheel rigidity Masked facies
Eye disorders		Oculogyric crisis Visual disturbance	Vision blurred		
Cardiac disorders			Tachycardia		Ventricular fibrillation Torsade de pointes

					Ventricular tachycardia Extrasystoles
Vascular disorders		Hypotension Orthostatic hypotension			
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm	Laryngeal oedema Laryngospasm
Gastrointestinal disorders		Vomiting Nausea Constipation Dry mouth Salivary hypersecretion			
Hepatobiliary disorders		Liver function test abnormal	Hepatitis Jaundice		Acute hepatic failure Cholestasis
Skin and subcutaneous tissue disorders		Rash	Photosensitivity reaction Urticaria Pruritus Hyperhidrosis		Angioedema Dermatitis exfoliative Leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders			Torticollis Muscle rigidity Muscle spasms Musculoskeletal stiffness	Trismus Muscle twitching	Rhabdomyolysis
Renal and urinary disorders		Urinary retention			
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		Erectile dysfunction	Amenorrhoea Galactorrhoea Dysmenorrhoea Breast pain Breast discomfort	Menorrhagia Menstrual disorder Sexual dysfunction	Priapism Gynaecomastia
General disorders and administration site conditions			Hyperthermia Oedema Gait disturbance		Sudden death Face oedema Hypothermia

Investigations		Weight increased Weight decreased		Electrocardiogram QT prolonged	

Electrocardiogram QT prolonged, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), torsade de pointes and sudden death have been reported with haloperidol.

Class effects of antipsychotics
Cardiac arrest has been reported with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotics. The frequency is unknown.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
The manifestations of haloperidol overdose are an exaggeration of the known pharmacological effects and adverse reactions. The most prominent symptoms are severe extrapyramidal reactions, hypotension and sedation. An extrapyramidal reaction is manifest by muscular rigidity and a generalised or localised tremor. Hypertension rather than hypotension is also possible.

In extreme cases, the patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QTc prolongation, must be considered.

Treatment
There is no specific antidote. Treatment is supportive. The efficacy of activated charcoal has not been established. Dialysis is not recommended in the treatment of overdose because it removes only very small amounts of haloperidol (see section 5.2).

For comatose patients, a patent airway must be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration.

It is recommended that ECG and vital signs be monitored, and that monitoring continues until the ECG is normal. Treatment of severe arrhythmias with appropriate anti-arrhythmic measures is recommended.

Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma or concentrated albumin and vasopressor agents, such as dopamine or noradrenaline. Adrenaline must not be used because it might cause profound hypotension in the presence of haloperidol.

In cases of severe extrapyramidal reactions, parenteral administration of an antiparkinson medicinal product is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; antipsychotics; butyrophenone derivatives: ATC code: NO5A DO1

Mechanism of action
Haloperidol is an antipsychotic belonging to the butyrophenones group. It is a potent central dopamine type 2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects
Haloperidol suppresses delusions and hallucinations as a direct consequence of blocking dopaminergic signalling in the mesolimbic pathway. The central dopamine blocking effect has activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes.

The activity on the basal ganglia probably underlies the undesirable extrapyramidal motor effects (dystonia, akathisia and parkinsonism).
The antidopaminergic effects of haloperidol on lactotropes in the anterior pituitary explain hyperprolactinaemia due to inhibition of dopamine-mediated tonic inhibition of prolactin secretion.

5.2 Pharmacokinetic properties

Absorption
The average bioavailability of haloperidol after administration of the tablet is 60 to 70%. Peak plasma levels of haloperidol are generally attained within 2 to 6 hours of oral dosing. A high inter-subject variability in plasma concentrations was observed. Steady state is reached within 1 week of treatment initiation.

Distribution
Mean haloperidol plasma protein binding in adults is approximately 88 to 92%. There is a high inter-subject variability for plasma protein binding. Haloperidol is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (mean values 8 to 21 l/kg after intravenous dosing). Haloperidol crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation
Haloperidol is extensively metabolised in the liver. The main metabolic pathways of haloperidol in humans include glucuronidation, ketone reduction, oxidative N-dealkylation and formation of pyridinium metabolites. The metabolites of haloperidol are not considered to make a significant contribution to its activity; however, the reduction pathway accounts approximately for 23% of the biotransformation, and back-conversion of the reduced metabolite of haloperidol to haloperidol cannot be fully ruled out. The cytochrome P450 enzymes CYP3A4 and CYP2D6 are involved in haloperidol metabolism. Inhibition or induction of CYP3A4, or inhibition of CYP2D6, may affect haloperidol metabolism. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations.

Elimination
The terminal elimination half-life of haloperidol is on average 24 hours (range of means 15 to 37 hours) after oral administration. Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 l/h/kg and is reduced in poor metabolisers of CYP2D6. Reduced CYP2D6 enzyme activity may result in increased concentrations of haloperidol. The inter-subject variability (coefficient of variation, %) in haloperidol clearance was estimated to be 44% in a population pharmacokinetic analysis in patients with schizophrenia. After intravenous haloperidol administration, 21% of the dose was eliminated in the faeces and 33% in the urine. Less than 3% of the dose is excreted unchanged in the urine.

Linearity/non-linearity
A linear relationship exists between haloperidol dose and plasma concentrations in adults.

Special populations

Elderly
Haloperidol plasma concentrations in elderly patients were higher than in younger adults administered the same dose. Results from small clinical studies suggest a lower clearance and a longer elimination half-life of haloperidol in elderly patients. The results are within the observed variability in haloperidol pharmacokinetics. Dose adjustment is recommended in elderly patients (see section 4.2).

Renal impairment
The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. About one-third of a haloperidol dose is excreted in urine, mostly as metabolites. Less than 3% of administered haloperidol is eliminated unchanged in the urine. Haloperidol metabolites are not considered to make a significant contribution to its activity, although for the reduced metabolite of haloperidol, back-conversion to haloperidol cannot be fully ruled out. Even though impairment of renal function is not expected to affect haloperidol elimination to a clinically relevant extent, caution is advised in patients with renal impairment, and especially those with severe impairment, due to the long half-life of haloperidol and its reduced metabolite, and the possibility of accumulation (see section 4.2).

Because of the high haloperidol distribution volume and its high protein binding, only very small amounts are removed by dialysis.

Hepatic impairment
The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. However, hepatic impairment may have significant effects on the pharmacokinetics of haloperidol because it is extensively metabolised in the liver. Therefore, dose adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 and 4.4).

Paediatric population
Limited plasma concentration data were established in paediatric studies including 78 patients with various disorders (schizophrenia, psychotic disorder, Tourette's syndrome, autism) who received oral haloperidol doses up to a maximum of 30 mg/day. These studies included mainly children and adolescents aged between 2 and 17 years. Plasma concentrations measured at various time points and after various durations of treatment, were either undetectable or ranged up to a maximum of 44.3 ng/ml. As in adults, high inter-subject variability in plasma concentrations was observed. There was a trend toward shorter half-lives in children compared to adults.

In 2 studies in children receiving haloperidol treatment for tics and Tourette's syndrome, a positive response was associated with plasma concentrations of 1 to 4 ng/ml.

Pharmacokinetic/pharmacodynamics relationships

Therapeutic concentrations
Based on published data from multiple clinical studies, therapeutic response is obtained in most patients with acute or chronic schizophrenia at plasma concentrations of 1 to 10 ng/ml. A subset of patients may require higher concentrations as a consequence of a high inter-subject variability in haloperidol pharmacokinetics.

In patients with first-episode schizophrenia, therapeutic response may be obtained at concentrations as low as 0.6 to 3.2 ng/ml, as estimated based on measurements of D_2 receptor occupancy and assuming that a D_2 receptor occupancy level of 60 to 80% is most appropriate for obtaining therapeutic response and limiting extrapyramidal symptoms. On average, concentrations in this range would be obtained with doses of 1 to 4 mg daily.

Due to the high inter-subject variability in haloperidol pharmacokinetics and the concentration-effect relationship, it is recommended to adjust the individual haloperidol dose based on the patient's response, taking into account data suggesting a lag time of 5 days to reach half of the maximal therapeutic response. Measurement of haloperidol blood concentrations may be considered in individual cases.

Cardiovascular effects
The risk of QTc prolongation increases with haloperidol dose and with haloperidol plasma concentrations.

Extrapyramidal symptoms
Extrapyramidal symptoms can occur within the therapeutic range, although the frequency is usually higher with doses producing higher than therapeutic concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of repeat dose toxicity and genotoxicity. In rodents, haloperidol administration showed a decrease in fertility, limited teratogenicity as well as embryo-toxic effects.

In a carcinogenicity study of haloperidol, dose-dependent increases in pituitary gland adenomas and mammary gland carcinomas were seen in female mice. These tumours may be caused by prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

Haloperidol has been shown to block the cardiac hERG channel in several published studies *in vitro*. In a number of *in vivo* studies, intravenous administration of haloperidol in some animal models has caused significant QTc prolongation at doses around 0.3 mg/kg, producing C_{max} plasma levels at least 7 to 14 times higher than the therapeutic plasma concentrations of 1 to 10 ng/ml that were effective in the majority of patients in clinical studies. These intravenous doses, which prolonged QTc, did not cause arrhythmias. In some animal studies, higher intravenous haloperidol doses of 1 mg/kg or greater caused QTc prolongation and/or ventricular arrhythmias at C_{max} plasma levels at least 38 to 137 times higher than the therapeutic plasma concentrations that were effective in the majority of patients in clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised starch
Magnesium stearate
Erythrosine Lake (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original container.

6.5 Nature and contents of container

PVC/Aluminium blisters in packs of 30 or 100 tablets.
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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. <? xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />

7 MARKETING AUTHORISATION HOLDER

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