September 10, 2017

Translation of the Danish summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISICS

for

Haloperidol/Serenase, injection

0. D.SP.NR.
01907

1. NAME OF THE MEDICINAL PRODUCT
Haloperidol/Serenase

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml contains 5 mg haloperidol.

All excipients are listed in section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

Clear, colorless solution, free of visual particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Psychotic conditions except depressions.

4.2 Posology and method of administration
Haloperidol injection solution should preferably be administrated intramuscularly, but when this is not appropriate intravenous injection may be used.

The below mentioned doses are only average doses; Dosage should be adjusted to the individual patient's response. This usually involves dose escalation in the acute phase and gradual reduction in the maintenance phase to estimate the minimum dose that is clinically effective. Higher doses should only be administered to patients who are non-responders to lower doses.

Adults:
The maximum daily dose is 20 mg. Doses of 5 mg should be administered intramuscularly and may be repeated every hour, until satisfactory clinical response, or to a maximum of 20 mg daily.

Pediatric population:
The safety and efficacy of haloperidol in the pediatric population is not clear.

4.3 Contraindications

Hypersensitivity to haloperidol, or to any of the excipients in section 6.1.
Comatose states
CNS depression caused by alcohol, or other drugs with CNS depression potential.
Parkinsonism
Extrapyramidal diseases
Clinically significant cardiac disorders
Prolongation of
Previous ventricular arrhythmia
Torsade de pointes
Uncorrected hypokalaemia
Concomitant administration with other QT-prolonging drugs.

4.4 Special warnings and precautions for use

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo- controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, 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 drug- treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death 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, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Patients with the following disorders/conditions should be closely monitored during treatment:
Cardiovascular conditions, bradycardia, hypokalaemia or a family history of QT-prolongation, due to the risk of further prolongation of the QT-syndrome, which may increase risk of developing torsade de pointes, tachycardia and sudden death. Very rare reports of QT-prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.
The risk of QT-prolongation and/or ventricular arrhythmias may be increased with parenteral administration, particularly intravenous administration.
Continuous ECG monitoring should be performed for QT-prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously.
Baseline ECG is recommended prior to treatment in all patients, (see section 4.3).
During therapy, the need for ECG monitoring should be assessed on an individual basis. During therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QT-interval exceeds 500ms.
Periodic electrolyte monitoring is recommended.
Renal failure
Pheochromocytoma
Epilepsy and in conditions predisposing to convulsions (e.g. alcohol withdrawal and brain damage). Due to the risk of reducing seizure threshold and triggering convulsions.
In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.
Tachycardia and hypotension have been observed in some patients.
When depression and psychosis occur at the same time, treatment should be combined with antidepressants (see section 4.5. for TCA).

Gradual withdrawal is advisable to avoid acute withdrawal symptoms including nausea, vomiting and insomnia.

Concomitant treatment with other antipsychotics should be avoided.

Neuroleptic malignant syndrome
In common with other antipsychotic drugs, haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased levels of creatine phosphokinase. Hyperthermia is often an early sign of this syndrome. If the described symptoms occur haloperidol should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia
As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. 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 dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Extrapyramidal symptom
In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia and acute dystonia.
Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant antiparkinson medication 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 physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

Hepatobiliary concerns
As haloperidol is metabolised by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.

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

Venous thromboembolism
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 haloperidol and preventive measures undertaken.

Increased mortality in elderly with dementia
Data from two large observational studies have shown an increased risk of death among elderly patients with dementia treated with antipsychotics, compared with elderly with dementia not treated with antipsychotics. There is not sufficient data to give an estimate of the magnitude of the increased risk and the causality of the increased mortality is not known.

Haloperidol is not licensed for the treatment of dementia-related behavioural disturbances.

Pediatric population
Data regarding safety in the pediatric population show a risk of extrapyramidal symptoms, including tardive dyskinesia and sedation. There is no long-term safety data available.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhea, gynecomastia and oligo- or amenorrhea. Very rare cases of hypoglycaemia and of Syndrome of Inappropriate ADH Secretion have been reported.

4.5 Interactions with other medicinal products and other forms of interaction.
There is a potential risk of interaction with concomitant use of metabolic inhibitors, drugs known to prolong QT-interval or cause electrolyte disturbances.

Haloperidol is metabolised by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse reactions, including QT-prolongation.

In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterised as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, venlafaxine, alprazolam, fluvoxamine, fluoxetine, sertraline, chlorpromazine, quinidine, itraconazol and promethazine. A decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations.
Increased haloperidol concentrations may increase the risk of QT-interval prolongation and it may be necessary to reduce the haloperidol dosage.
Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400mg/day) and paroxetine (20mg/day).

Caution should be applied if haloperidol is used in combination with drugs known to cause electrolyte imbalances.

Effect of other drugs on haloperidol
When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicin is added to haloperidol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the haloperidol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of haloperidol.

Sodium valproate, a drug known to inhibit glucorinidation, does not affect haloperidol plasma concentrations.

Effects of haloperidol on other drugs
In common with all neuroleptics, haloperidol can increase the central nervous system depression produced by other CNS-depressing drugs, including alcohol, hypnotics, sedatives or potent analgesics (see section 4.4).

Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood-pressure-lowering effects of adrenergic-blocking agents such as e.g. guanethidine.

Haloperidol may impair the antiparkinsonistic effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants, thereby increasing plasma levels of these drugs.

Other types of interaction
Caution should be applied when concomitant use of haloperidol and drugs known to induce hypokalaemia, e.g. diuretics and laxatives.

Fluvoxamine (repeated dosage) increases plasma concentration of haloperidol, hereby increasing haloperidol's antipsychotic effect on patients with schizophrenia. Increase in plasma concentration is dose-dependent.

Concomitant treatment with orphenadrine increases plasma concentration of haloperidol, and thereby increases the risk of extrapyramidal symptoms. It may be necessary to reduce dosage of haloperidol.

Concomitant treatment with methyldopa has shown an increased CNS effect.

Concomitant use of haloperidol and lithium may increase the risk of neurotoxic adverse reaction, if such symptoms occur haloperidol should be stopped immediately.

4.6 Pregnancy and lactation

Pregnancy
Animal studies have shown harmful effects on reproduction (see section 5.3.)

Neonates exposed to antipsychotics (including haloperidol) during 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, newborns should be monitored carefully
Haloperidol may be used during pregnancy only if the anticipated benefit for the mother outweighs the possible risks to the fetus.

In population studies, no significant increase in birth defects was found.
In isolated cases, there have been reports on birth defects following fetal exposure to haloperidol.

Lactation
Haloperidol should only be used during lactation on compelling indication.
Haloperidol is excreted in breast milk.
Extrapyramidal symptoms have been observed in breast-fed children by women treated with haloperidol.

4.7 Effects on ability to drive and use machines

No mark.

Haloperidol may, particularly with higher doses and at start of treatment, affect the ability to drive or use machines to a lesser or moderate extent.

4.8 Undesirable reactions

The safety of haloperidol was evaluated in 284 haloperidol-treated subjects who participated in 3 placebo-controlled, and in 1295 haloperidol-treated subjects who participated in sixteen double-blind active comparator-controlled clinical trials. The safety of haloperidol decanoate was evaluated in 410 subjects who participated in 3 comparator trials (one comparing haloperidol vs. fluphenazine and two comparing the decanoate formulation to the oral formulation), 9 open label trials and 1 dose response trial. Based on pooled safety data from these clinical trials, the most commonly reported (% incidence) Adverse Drug Reactions (ADRs) were: extrapyramidal disorder (34), insomnia (19), agitation (15), hyperkinesia (13), headache (12), psychotic disorder (9), depression (8), weight increases (8), orthostatic hypotension (7) and somnolence (5).

Including the above mentioned adverse reactions, the following adverse reactions have been observed from clinical trials and post-marketing experiences reported with the use of haloperidol and haloperidol Decanoate.

Frequencies displayed use 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).

Investigations Common Rare	 Weight gain, weight loss. Prolonged QT-interval on ECG.
Heart Uncommon Not known	 Tachycardia. Ventricular fibrillation, torsade de pointes, ventricular tachycardia.
Blood and lymphatic system Very rare Not known	 Leukopenia. Agranulocytosis, neutropenia, pancytopenia, trombocytopenia.
Nervous system Very common Common	 Ekstrapyramidal symptoms, hyperkinesia, Headache Tardiv dyskinesia, oculogyric crisis, dystonia, dyskinesia, akathisia, bradykinesia, hypokinesia, hypertonia, somnolence, masked facies, tremor, dizziness.

Uncommon (1/1.000 til 1/100) Rare	Convulsion, parkinsonism, akinesia, cogwheel rigidity, sedation, involuntary muscle contractions. Motoric dysfunction, neuroleptic malignant syndrome, nystagmus.
Eyes Common Uncommon (1/1.000 til 1/100)	 Visual disturbance Blurred vision
Gastrointestinal Common	 Constipation, dry mouth, salivary hypersecretion, nausea, vomiting.
Kidneys and urinary tract Common	 Urinary retention.
Skin and subcutaneous tissue Common Uncommon Not known	 Rash. Photosensitivity reaction, urticaria, pruritus, hyperhidrosis. Leukocytoclastic vasculitis, exfoliative dermatitis.
Musculoskeletal and connective tissue Uncommon Rare	 Torticollis, muscle rigidity, muscle spasms, Musculoskeletal stiffness. Trismus, muscle twitching.
The endocrine system Rare Not known	 Hyperprolactinaemia. Inappropiate antidiuretic hormone secretion
Metabolism and nutrition Not known	 Hypoglycemia
Vascular disorders Common	 Orthostatic hypotension, hypotension.
Respiratory, thoracic and mediastinal disorders Uncommon Rare Not known	 Dyspnea Bronchospasm Laryngeal edema, laryngospasm.
General disorders and administration site condition Uncommon Not known	 Gait disturbances, hyperthermia, edema. Sudden Death, facial edema, hypothermia.

Immune system Uncommon Not Known	 Hypersensitivity. Anaphylactic reaction.
Hepatobilliary disorders Common Uncommon Not known	 Abnormal liver function Hepatitis, jaundice. Acute hepatic failure, cholestasis.
Pregnancy, puerperium and perinatal disorders Not known	 Neonatal drug withdrawal syndrome (see 4.6)
Reproductive system and breast disorders Common Uncommon Rare Not known	 Erectile dysfunction. Amenorrhea, dysmenorrhea, galactorrhea, breast discomfort, breast pain. Menorrhagia, menstrual disorders, sexual dysfunction. Gynecomastia, priapism.
Psychiatric disorders Very common Common Uncommon	 Agitation, nsomnia. Depression, Psychotic disorders Confusional state, decreased libido, loss of libido, restlessness

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported during treatment with antipsychotic drugs (frequency 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 to:

Sundhedsstyrelsen
Axel Heides Gade 1,
DK-2300 København S.
Websted: www.meldenbivirkning.dk.
E-mail: sst@sst.dk.

4.9 Overdose

Symptoms:

Increased amount of known pharmacological effects and adverse reaction. The most prominent symptoms are: severe extrapyramidal symptoms, hypotension and sedation. Hypertension may occur.

In extreme cases, the patient may appear comatose with respiratory depression and hypotension, which could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias possible associated with QT-prolongation should be considered.

Treatment

There is no specific antidote to haloperidol. Treatment is mainly supportive measures. Activated charcoal may be administered.

In comatose patients a patent airway should be established. Mechanically assisted ventilation may be needed due to respiratory depression.

ECG and vital signs should be monitored until ECG is normalized. Severe arrhythmia should be treated anti-arrhythmic agents.

Hypotension and circulatory collapse should be treated by intravenous administration of fluids, plasma or concentrated albumin and vasopressors like dopamine or noradrenaline. Adrenaline should not be used, since it may cause severe hypotension with concomitant use of haloperidol.

In cases of severe extrapyramidal symptoms, appropriate parenteral antiparkinson medication should be administered.

4.10 Extradition

B

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification

ATC-code: N 05 AD 01. Psycholeptics, antipsychotics, butyrophenon.

5.1 Pharmacodynamic properties

Haloperidol is a neuroleptic belonging to the group of butyrophenones. Haloperidol is a potent central dopamine antagonist and thereby classified among the very incisive neuroleptics. Haloperidol has no antihistamine- or anticholinergic properties. Because of the central dopamine antagonism, haloperidol has a compendious effect on delusions and imaginations (possibly caused by an interaction of the mesocortic and limbic system) and activity in the basal ganglia. Haloperidol causes an effective psychomotoric sedation, which explains the effect on mania and other behavioral-motoric syndromes. The influence on the basal ganglia possibly explains the extrapyramidal symptoms (dystonia, akathisia and parkinsonism). The effect on peripheral dopamine receptors explains the effect on nausea and vomiting (through the chemoreceptor trigger zone), the gastro-intestinal relaxation and increased secretion of prolactin (through inhibition of PIF, prolactin inhibiting factor, at the anterior pituitary gland level).

5.2 Pharmacokinetic properties

Absorption

The bioavailability of the drug is 60-70% when administered orally. Haloperidol's C_{max} appear within 2-6 hours after oral administration and within 20 minutes after intramuscular administration.

Distribution

92% of the drug is bound to plasma proteins. The distribution volume at steady state (Vd_{ss}) is large (7,9 l/kg). Haloperidol passes the blood-brain barrier.

Metabolization

Haloperidol is metabolized through various systems including cytochrome P450 (especially CYP3A4 and CYP 2D6) and glucoronidation.

Elimination

The average half-life in plasma (terminal elimination) is 24 hours (range 12-38 hours) after oral administration and 21 hours (range 13-36 hours) after intramuscular administration. Excretion is through feces (60%) and urine (40%). Approximately 1% of haloperidol is excreted unaffected in the urine.

Therapeutic concentrations

The proposed plasma concentration needed to reach a therapeutic response lies between 4 μg/L and a maximum of 20-25 μg/L.

5.3 Preclinical safety data

Preclinical data show no increased risk in humans based on conventional research on toxicology after repeated doses, genotoxicity and carcinogenicity. In rodents, exposure to haloperidol showed a decreased fertility and limited reproductive toxicity and embryo-toxic effects.

Haloperidol has been shown to block the cardiac hERG channel in several published *in vitro* studies. 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 i.v., giving C_{max} plasma levels 3 to 7 times higher than the effective human plasma concentrations of 4 to 20 ng/ml. These intravenous doses which prolonged QTc did not cause arrhythmias. In some studies, higher intravenous doses of 1 to 5 mg/kg haloperidol i.v. caused QTc prolongation and/or ventricular arrhythmias at C_{max} plasma levels 19 to 68 times higher than the effective human plasma concentrations.

6. FARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Water for Injections

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

5 years.

6.4 Special precautions for storage
No specific requirements for storage.

6.5 Nature and contents of container
Ampules

6.6 Special precautions for disposal and handling
Ampules should be disposed in appropriate packaging e.g. needle container.

7. MARKETING AUTHORISATION HOLDER
Janssen-Cilag A/S
Bregnerødvej 133
3460 Birkerød

8. MARKETING AUTHORISATION NUMBER(S)
09661

9. DATE OF FIRST AUTHORISATION APPROVAL
21. July 1959

10. DATE OF REVISION OF THE TEXT
6. July 2015