Core Safety Profile

Active substance:	**Bromperidol decanoate**
Pharmaceutical form(s)/strength:	**50 mg/ml solution for injection**
P-RMS:	**NL/H/PSUR/0041/001**
Date of FAR:	**26.08.2011**

4.3 Contraindications

/.../ DECANOATE is contraindicated in central nervous system depression, comatose states and in individuals who have previously displayed hypersensitivity to any of the ingredients of the injection solution or to another butyrophenone.

/.../ DECANOATE should not be used in depressive disorders or Parkinson's syndrome.

4.4 Special warnings and special precautions for use

Sudden death in patients receiving antipsychotic drugs

Cases of sudden and unexplained death have been reported in psychiatric patients receiving antipsychotic drugs, including bromperidol-containing products.

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 are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Venous Thromboembolism (VTE)

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 /.../ DECANOATE and preventive measures undertaken

Cerebrovascular Adverse Events (CVA)

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. /.../ DECANOATE should be used with caution in patients with risk factors for stroke.

Cardiovascular effects

Use with caution in patients with cardiovascular disease or family history of QT prolongation and avoid concomitant use of other neuroleptics.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, /.../ DECANOATE has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic

treatment 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 characterized by rhythmical 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 symptoms

In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia.

Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure.

It is recommended that patients being considered for /.../ DECANOATE therapy should initially be put on oral bromperidol to exclude the possibility of an unexpected adverse sensitivity to bromperidol.

/.../ DECANOATE should be used with caution in patients with hepatic dysfunction.

/.../ DECANOATE may lower the convulsive threshold and should therefore be used with caution in epileptic patients. If necessary the dose of the anticonvulsive therapy must be adapted in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

As with other antipsychotics, caution is advised when prescribing bromperidol decanoate with medications known to prolong the QT interval.

Caution is advised when used in combination with drugs known to cause electrolyte imbalance.

Effect of other drugs on bromperidol decanoate

Liver-enzyme induction by drugs (e.g., phenobarbital, carbamazepine, phenytoin) may potentiate the metabolisation of neuroleptics. Therefore during combination treatment, the bromperidol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of bromperidol.

In a pharmacokinetic study, increased bromperidol concentrations have been reported when bromperidol was given concomitantly with itraconazole known as a potent inhibitor of CYP 3A4.

Effect of bromperidol decanoate on other drugs

As with the use of other neuroleptics, bromperidol may potentiate sedation caused by other drugs (e.g. barbiturates, benzodiazepines, antihistamines) and by alcohol. It may also increase the risk of hypotension in patients using an antihypertensive. Bromperidol inhibits the action of dopamine agonists, such as bromocriptine, lisuride and L-dopa.

4.6 Pregnancy and lactation

Teratogenicity was not found in rats and rabbits. Neither have there been reports of birth defects in humans following fetal exposure to bromperidol-containing products, but safety in pregnant women has not been unequivocally established. When there is a need to administer /.../ DECANOATE during pregnancy the risks should be weighed carefully against the expected therapeutic benefits.

In rats bromperidol is excreted in breast milk. If the use of /.../ DECANOATE is considered essential, the benefits of breast-feeding should be balanced against its risks.

4.7 Effects on ability to drive and use machines

Patients who drive or operate machinery should be warned of the possibility of drowsiness and impaired mental alertness. Simultaneous intake of alcohol may potentiate these effects.

4.8 Undesirable effects

The safety of /.../ DECANOATE was evaluated in 93 subjects who participated in 6 open label clinical trials.

The safety of /.../ was evaluated in 128 subjects (65 subjects who received /.../, 63 subjects who received placebo) who participated in 2 placebo-controlled, double-blind clinical trials. Based on pooled safety data from these clinical trials, the most commonly reported (≥ 10% incidence) Adverse Drug Reactions (ADRs) were (with % incidence):

Endocrine Disorders: Hyperprolactinaemia (10);

Nervous System Disorders: Somnolence (32), Dizziness (29), Extrapyramidal disorders (28), Akathisia (28), Tremor (22), Dystonia (20), Hypertonia (10);

Psychiatric Disorders: Insomnia (19), Agitation (18);

Eye Disorders: Vision blurred (25);

Gastrointestinal Disorders: Dry mouth (20), Constipation (14), Salivary hypersecretion (12);

Musculoskeletal, Connective Tissue and Bone Disorders: Muscle rigidity (31);

Cardiac Disorders: Tachycardia (12);

General Disorder and Administration Site: Asthenia (15), Fatigue (12)

Including the above mentioned ADRs, the following table (next page) displays ADRs that have been reported with the use of /.../ DECANOATE and /.../ from either clinical trial or post marketing experiences. The displayed frequency categories 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.

System Organ Class	Adverse Drug Reactions				
	Frequency Category				
	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)	**Not Known**
Blood and lymphatic system disorders					Leukopenia; Thrombocytopenia
Endocrine disorders	Hyperprolactinaemia				Inappropriate antidiuretic hormone secretion
Psychiatric disorders	Agitation; Insomnia	Depression; Sleep disorder			
Nervous system disorders	Somnolence; Dizziness; Akathisia; Extrapyramidal disorder; Tremor; Dystonia; Hypertonia	Parkinsonism Akinesia; Hypokinesia; Dyskinesia; Sedation; Aphasia; Cogwheel rigidity; Ataxia	Headache		Convulsion; Neuroleptic malignant syndrome; Tardive dyskinesia
Eye disorders	Vision blurred	Oculogyric crisis			
Cardiac disorders	Tachycardia	Bradycardia			
Gastrointestinal disorders	Dry mouth; Constipation; Salivary hypersecretion	Nausea; Vomiting			
Hepatobiliary disorders					Hepatitis toxic; Liver function test increased
Skin and subcutaneous tissue disorders					Dermatitis allergic; Drug eruption
Musculoskeletal and connective tissue disorders	Muscle rigidity				Rhabdomyolysis
Renal and urinary disorders					Urinary retention
Reproductive system and breast disorders			Breast discharge		Gynaecomastia,
General disorders and administration site conditions	Asthenia; Fatigue				Sudden death; Pyrexia
Investigations		Electrocardiogram abnormal; Electroencephalogram abnormal; Weight increased			

Hormonal effects of antipsychotic neuroleptic drugs including hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea.

Hypotension has been reported in patients taking antipsychotic neuroleptic drugs, including bromperidol-containing products.

QT prolongation, Ventricular arrhythmias, Cardiac Arrest and Torsades de Pointes have been reported in patients who have been treated with bromperidol-containing products. While the information from these reports provided insufficient evidence to include these events as ADRs, these adverse effects are considered class effects of neuroleptics.

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

Overdosage is less likely to occur with parenteral than with oral medication. Information pertaining to oral /.../ is presented below.

Symptoms

In general, the symptoms of overdosage are an extension of the pharmacological effects. Extrapyramidal signs and symptoms predominate: oculogyric crisis, salivation, muscle rigidity, akinesia, akathisia. Drowsiness may occur. Some excitation is possible. The risk of cardiac arrhythmias should be considered.

Treatment

There is no specific antidote. Treatment should consist of supportive and symptomatic treatment. Extrapyramidal symptoms should be treated with an antiparkinsonian drug of the anticholinergic type as long as required.