# 1. PRODUCT NAME

**Droperidol Panpharma**, solution for injection 0.5 mg/mL and 2.5 mg/mL

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Droperidol Panpharma Injection contains either 0.5 mg/mL or 2.5 mg/mL droperidol as the active ingredient. Sodium hydroxide is present to adjust the pH to 3.4 ± 0.2.

For the full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Droperidol Panpharma Injection 0.5 mg/mL is presented as a 3 mL ampoule (filled with 2.5 mL); each ampoule contains 1.25 mg droperidol.

Droperidol Panpharma Injection 2.5 mg/mL is presented as a 1 mL ampoule; each ampoule contains 2.5 mg droperidol and 2 mL ampoule; each ampoule contains 5.0 mg droperidol.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

**Droperidol is only indicated in adults.**

Droperidol is indicated for the following conditions provided certain precautions are taken (see 4.3 Contraindications, 4.4 Special warnings and precautions for use):

***Anaesthesia***

Droperidol may be used to produce tranquilisation and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures. It can also be used for premedication, induction, and as an adjunct in the maintenance of general and regional anaesthesia

In neuroleptanalgesia, Droperidol can be given concurrently with a narcotic analgesic, such as fentanyl injection, to aid in producing tranquillity and in decreasing anxiety and pain.

Provided that certain precautions are taken, Droperidol may be administered as a neuroleptic in all types of surgical interventions.

The indications of choice for neuroleptanalgesia with Droperidol are major and prolonged surgery, interventions involving high risk for the patient or in aged persons, surgery in patients with a poor overall condition, and in individuals who are in shock.

***Psychiatry***

Droperidol may be used in the management of severe agitation, hyperactivity, or aggressiveness in psychotic disorders, including schizophrenic reaction and the manic type of manic depressive disorder, or in disturbed states, such as some types of acute brain syndrome and in non-psychotic acute excitation states.

## 4.2 Dose and method of administration

**Intravenous (IV) and Intramuscular (IM) use:**

| Volume | 0.5 mg/1mL equivalent |
|---|---|
| 2.5 mL | 1.25 mg |

| Volume | 2.5 mg/1mL equivalent |
|---|---|
| 1 mL | 2.5 mg |
| 2 mL | 5 mg |
| 3 mL | 7.5 mg |

The dosage should be adapted to each individual case. The factors to be considered here include age, body weight, the use of other medications, the type of anaesthesia to be used and the surgical procedure involved.

Vital signs should be monitored routinely. To minimise the risk of ventricular arrhythmia, an electrocardiograph (ECG) should be performed and examined for evidence of QT prolongation before any operation commences. ECG monitoring should continue during the surgical procedure and subsequently for a period of time consistent with best medical judgement. This should be at least 7 hours after the end of the procedure (see 4.3 Contraindications, 4.4 Special warnings and precautions for use).

Elderly or debilitated patients or individuals with previously reported adverse reactions to neuroleptic agents may require less Droperidol, and half the normal starting dose may be sufficient for a therapeutic response.

***Anaesthesia***

**Usual adult dosage:**

***Premedication and diagnostic use:***
2.5mg to 5mg may be administered intramuscularly or slowly intravenously 30 to 60 minutes before the diagnostic procedure. This (or a lower) dose will reduce the incidence of post- operative nausea and vomiting. The dosage should be reduced as appropriate in the elderly.

***Adjuvant to general anaesthesia:***
Induction: 2.5 mg per 10 kg may be administered (usually intravenously). Smaller doses may be adequate (see 4.4 Special warnings and precautions for use).

Maintenance (if required): 1.25 to 2.5 mg usually intravenously. An adequate circulation volume should be ensured in view of the alpha-blocking properties of droperidol.

**Adjuvant to regional anaesthesia:**
2.5 to 5 mg may be administered intramuscularly or slowly intravenously when additional sedation is required.

Usual paediatric dosage: For children, a reduced dose as low as 1.0 mg per 10 kg is recommended for premedication or anaesthesia induction.

***Psychiatry***

In psychiatry, the dosage should be determined on an individual basis and is best initiated and titrated under close clinical supervision. To determine the initial dose, the patient's age, the symptom severity, and the previous response to other neuroleptic agents should be taken into account.

**Adults:**
5 to 15 mg intravenously or up to 10 mg intramuscularly. The dosage may be repeated at intervals of 4 to 8 hours (intravenous or intramuscular).

**Children:**
0.5 to 1 mg/day intramuscularly adjusted according to their response.

**Elderly:**

Elderly or debilitated patients or individuals with a history of adverse reactions to neuroleptic agents may require less Droperidol and half the normal starting dose in psychiatry may be sufficient for a therapeutic response. The optimal response in such patients is usually obtained with more gradual titration and at lower doses. In adolescents, a lower starting dose may be recommended.

## 4.3 Contraindications

Droperidol is contraindicated in patients with known hypersensitivity to the agent or its metabolites, in patients with severe depression, in comatose individuals or in patients with Parkinson's disease.

Droperidol should not be used in female patients with a QTc of greater than 450 msec, or male patients with a QTc of greater than 440msec (see 4.4 Special warnings and precautions for use).

Droperidol is contraindicated in patients with acquired long QT interval, such as that associated with concomitant use of medicines known to prolong the QT interval (see 4.5 Interaction with other medicines and other forms of interactions), known hypokalaemia or hypomagnesaemia or clinically significant bradycardia. Droperidol is also contraindicated in patients with known congenital long QT interval or family history of congenital long QT syndrome.

## 4.4 Special warnings and precautions for use

The benefits of using Droperidol should be weighed against the potential risk. Droperidol should only be used under appropriate medical supervision.

Any patient subjected to anaesthesia and receiving potent CNS depressant agents or showing CNS depression should be monitored closely. Mild to moderate hypotension and occasionally (reflex) tachycardia have been observed following the administration of Droperidol. This reaction usually subsides spontaneously. However, should hypotension persist, the possibility of hypovolaemia should be considered and appropriate fluid replacement administered.

Patients with, or suspected of having, the following risk factors for cardiac arrhythmia should be carefully evaluated prior to the administration of Droperidol:

- a history of significant cardiac disease, including serious ventricular arrhythmia, second or third degree atrioventricular block, sinus node dysfunction, congestive heart failure or ischaemic heart disease and left ventricular hypertrophy.
- a family history of sudden death,
- renal failure (particularly with chronic dialysis),
- significant chronic obstructive pulmonary disease and respiratory failure,
- risk factors for electrolyte disturbances as seen in patients taking laxatives, glucocorticoids, potassium-wasting diuretics, in association with the administration of insulin in acute settings or in patients with persistent vomiting and/or diarrhoea.

In these patients, an ECG and an assessment of serum electrolytes (potassium and magnesium) and renal function should be performed as part of this evaluation and the presence of QT prolongation excluded prior to administration of droperidol. Continuous pulse oximetry should be performed in patients with identified or suspected risk of ventriculararrythmia and should continue for 30 minutes following single i.v. administration. In a hospital setting, ECG monitoring should be started, when possible, before the administration of Droperidol for anaesthesia (see 4.3 Contraindications). For patients with acute mania or agitation, it is recognised that performing an ECG prior to the initial dose(s) may be difficult. However, an ECG should be performed as soon as the patient's acute symptoms have subsided. Although the possibility of developing QT prolongation and torsade de

pointes with the use of Droperidol is low, ECG monitoring and full cardiac resuscitation facilities should be available.

Outside the hospital setting, Droperidol should only be used for the management of the psychiatric crisis (e.g. acute mania or severe agitation). A single injection should be administered, either intravenously (not greater than 2.5 mg) or intramuscularly (not greater than 5 mg) and the patient should then be transferred immediately to a hospital facility by an ambulance equipped for cardiac resuscitation. If additional sedation is required, a suitable acting sedative (such as a benzodiazepine) should be considered.

Patients with a history of alcohol abuse, or recent high intakes are at the risk of increased arrhythmia.

In patients with diagnosed or suspected pheochromocytoma, severe hyper-tension and tachycardia have been observed after administration of Droperidol. Therefore, the use of Droperidol should be avoided in such patients. Since Droperidol is metabolised extensively in the liver, the agent should be used with caution in patients with impaired hepatic function. Droperidol should also be used with care in patients suffering from severe depression or Parkinson's disease.

In the long-term treatment of psychiatric patients, the neuroleptic malignant syndrome may occur in very rare cases.

Caution is advised if Droperidol is given concomitantly with strong CYP1A2 and CYP3A4 inhibitors.

***Elderly patients with Dementia-related Psychosis***
Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age > 80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia an approximately 3-fold increase of cerebrovascular adverse events has 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. Droperidol should be used with caution in patients with risk factors for stroke.

Use with caution in patients with epilepsy (or a history of epilepsy) and conditions predisposing to epilepsy or convulsions.

***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 droperidol and preventive measures taken.

***Suicide***
The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy.

***Use in Children***
The safety of Droperidol in children younger than two years of age has not been established. Therefore, this agent is not recommended in this age group.

***Use in Elderly***
The initial dose of Droperidol should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.

## 4.5 Interaction with other medicines and other forms of interaction

Medicines known to prolong the QT interval are contraindicated with Droperidol. Examples include certain antiarrhythmics, such as those of Class IA (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol); tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as phenothiazines, pimozide and sertindole); certainantihistamines (such as astemizole and terfenadine); cisapride, bepridil, halofantrine and sparfloxacin.

Droperidol may potentiate the action of sedative agents (including barbiturates, benzodiazepines, morphinomimetics); the same applies to antihypertensive agents, whereby orthostatic hypotension may ensue. Like other sedative agents, Droperidol may potentiate respiratory depression caused by opioids.

Since Droperidol blocks dopamine receptors, it may inhibit the action of dopamine agonists, such as bromocriptine, lisuride and levodopa.

Concomitant use of Droperidol with CYP1A2 inhibitors and/or CYP3A4 inhibitors could decrease the rate of Droperidol metabolism and prolong its pharmacological action.

Theoretically, certain agents (e.g. phenobarbitone, carbamazepine, phenytoin), as well as smoking and alcohol consumption, which stimulate metabolising enzymes in the liver, may enhance the metabolic breakdown of neuroleptic agents, possibly necessitating adjustment of the dose.

## 4.6 Fertility, pregnancy and lactation

***Fertility***

The fertility data is not available.

***Pregnancy (Category C)***

Neonates exposed to antipsychotic drugs (including Droperidol) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

Droperidol should be used during pregnancy only if the anticipated benefit outweighs the risk, and the administered dose and duration of treatment should be as low and as short as possible.

Droperidol is not teratogenic in animals and has been used in a few isolated instances in pregnant women; as with all other pharmacological agents, the benefits of using Droperidol in these situations should be carefully weighed against the possible hazards.

***Lactation***

Butyrophenones are excreted in breast milk. If the use of Droperidol is essential, breast-feeding should be avoided.

## 4.7 Effects on ability to drive and use machines

Patients should only drive or operate a machine if sufficient time has elapsed after the administration of Droperidol, i.e. about 10 hours after a dose of up to 5 mg and 24 hours after higher doses.

## 4.8 Undesirable effects

***CNS Effects***

Droperidol may produce Parkinsonian or dyskinetic extrapyramidal side effects. These are readily and completely reversible by treatment with an anti-Parkinsonian agent of the anticholinergic type. In rare

cases, paradoxical reactions, including hallucinations, restlessness and isolated cases of anxiety and agitation have been observed.

***Neuroleptic Malignant Syndrome***
Like other neuroleptic agents, DROPERIDOL has been associated with rare cases of the neuroleptic malignant syndrome, a rarely occurring idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, and altered consciousness. Hyperthermia is often an early warning sign of this syndrome. In such cases, Droperidol treatment should be discontinued immediately and appropriate supportive therapy and careful monitoring should be initiated.

***Tardive Dyskinesia***
As with other neuroleptic agents, tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of treatment. The syndrome is mainly characterised by involuntary rhythmical movements of the tongue, face, mouth or jaw. The symptoms may persist 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 agent. Treatment should be discontinued as soon as possible.

***Cardiovascular Effects***
Mild to moderate hypotension and occasionally (reflex) tachycardia have been observed following administration of droperidol (see 4.4 Special warnings and precautions for use). Should hypotension persist, the possibility of hypovloaemia should be considered and appropriate fluid replacement administered. Cases of QT interval prolongation, ventricular arrhythmias and sudden death have been reported rarely. They may occur more frequently with high doses and in predisposed patients. Patients with a history of alcohol abuse or recent high intakes, are at the risk of increased arrhythmia.

***Endocrine Effects***
Hormonal effects of antipsychotic neuroleptic agents include cases of hyperprolactinaemia which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. Neonatal drug withdrawal syndrome has been associated with prolonged exposure in psychiatric indications. Very rare cases of Syndrome of Inappropriate ADH Secretion have been reported.

***Miscellaneous***
In rare cases, body temperature dysregulation and hypersensitivity reactions such as rash or angio-oedema and anaphylactic reactions have been reported. Other side effects include cardiac arrest, torsades de pointes and hyperglycaemia.

***Reporting of suspected adverse reactions***
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

***Symptoms***
The manifestations of Droperidol overdosage are an extension of its pharmacological actions. Symptoms of accidental overdosage are psychic indifference with a transition to sleep, sometimes in association with lowered blood pressure. At higher doses or in sensitive patients, extrapyramidal disorders may occur (salivation, abnormal movements, sometimes muscle rigidity). Convulsions may occur at toxic doses. Cases of QT-interval prolongation, ventricular arrhythmias and sudden death have been reported rarely.

***Treatment***

No specific antidote is known. However, when extrapyramidal reactions occur, an anticholinergic agent should be administered.

Immediate cardiac monitoring by ECG is recommended for any patient who has received an overdose of Droperidol. The ECG should be evaluated for possible QT-prolongation and the patient should be evaluated for factors that could predispose to the occurrence of torsade de pointes, such as electrolyte disturbances (especially hypokalaemia or hypomagnesaemia) and bradycardia.

Cases of profound hypotension should be treated by boosting circulation volume and taking other appropriate measures. In the event of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If required, the patient should be observed carefully for 24 hours or longer; body warmth and adequate fluid intake should be maintained.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Droperidol is a butyrophenone neuroleptic agent. Its pharmacological profile is characterised mainly by dopamine-blocking and α1-adrenolytic effects. Droperidol is devoid of anticholinergic and antihistaminic activity. It has a marked tranquilising and sedative effect, alleviates apprehension and causes a state of mental detachment and indifference while maintaining a state of reflex alertness.

Droperidol produces an antiemetic effect. It lowers the incidence of nausea and vomiting during surgical procedures and provides antiemetic protection in the postoperative period.

Droperidol potentiates other CNS depressants. It induces mild α1-adrenergic blockade and peripheral vascular dilatation and reduces the pressor effect of adrenaline. It can cause hypotension and decreased peripheral vascular resistance and may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may also reduce the incidence of adrenaline-induced arrhythmia, but it does not prevent other forms of cardiac arrhythmia.

## 5.2 Pharmacokinetic properties

The action of a single intramuscular and intravenous dose commences 3 to 10 minutes after administration, although the peak effect may not be apparent for up to 30 minutes. Tranquilising and sedative effects tend to persist for 2 to 4 hours, although alertness may be affected for up to 12 hours.

After intravenous administration, plasma concentrations fall rapidly during the first 15 minutes. Plasma protein binding is in the range of 85 to 90%. The distribution volume is 99 to 168 litres. 75% of the metabolites are eliminated via the kidneys. Only 1% of the agent is excreted unchanged in urine, and 11% in faeces. Plasma clearance is 570mL/min. The elimination half-life (t1/2) is 134 ± 13 minutes. The bioavailability of the oral form is 75%, the peak concentration being reached after 1 to 2 hours.

## 5.3 Preclinical safety data

Not available.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium hydroxide, water for injections, mannitol and tartaric acid.

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

## 6.3 Shelf life

3 years.

## 6.4 Special precautions for storage

Store below 25°C. Protect from light.

## 6.5 Nature and contents of container

Droperidol Panpharma Injection 0.5 mg/mL is presented as a 3 mL ampoule (filled with 2.5 mL) in a carton of 5 or 10 ampoules.

Droperidol Panpharma Injection 2.5 mg/mL is presented as a 1 mL ampoule in a carton of 5, 10 or 50 ampoules and a 2 mL ampoule in a carton of 5, 10 or 50 ampoules.

Product is for single use in one patient only. Discard any residue.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

# 7. MEDICINE SCHEDULE

Prescription medicine

# 8. SPONSOR

Multichem NZ Limited
8 Apollo Drive
Rosedale
Auckland 0632

Telephone: (09) 488 0330

# 9. DATE OF FIRST APPROVAL

N/A

# 10. DATE OF REVISION OF THE TEXT

30 June 2017

## SUMMARY TABLE OF CHANGES

| DATE | CHANGE |
|---|---|
| 30.06.2017 | New data sheet. |