NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Droleptan 2.5 mg in 1 mL Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains Droperidol as the tartrate equivalent to 2.5 mg of Droperidol base with pH 3.4 ± 0.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

Droleptan Injection 2.5 mg in 1 mL is a sterile, non-pyrogenic aqueous solution for intravenous or intramuscular injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Droleptan is indicated for the following conditions provided certain precautions are taken (see Contraindications, Warnings and Precautions):

Droleptan is indicated for the prevention and treatment of post-operative nausea and vomiting in adults and children (> 2 years of age).

Droleptan is indicated for the acute management of severe agitation, hyperactivity, or aggressiveness in adults, where the patient may cause injury to themselves or others for example, during a schizophrenic reaction, acute mania of bipolar disorder severely disturbed states. (See section 4.2).

4.2 Dose and method of administration

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

Prevention and treatment of post-operative nausea and vomiting

For intravenous use. Inject solution slowly.

Adults

Adults (18 – 65 years): 0.625 mg to 1.25 mg

Elderly (over 65 years): 0.625 mg

Renal/hepatic impairment: 0.625 mg

Children and adolescents (2 – 18 years of age)

10 to 50 microgram/kg (up to a maximum of 1.25 mg).

Use in children under 2 years of age is not recommended.

Droperidol is generally not first line treatment. Consult local guidelines.

Administration of Droperidol is recommended 30 minutes before the anticipated end of surgery. Repeat doses may be given every 6 hours as required.

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 (see section 4.4).

Acute management of severe agitation, hyperactivity, or aggressiveness in adults,

For acute severe episodes only if clearly necessary, and where the potential benefits outweigh the potential risks.

The dosage should be determined on an individual basis and given under close clinical supervision in a hospital setting with appropriate cardiac resuscitation available. 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:

2.5mg to 5mg given by intravenous or intramuscular injection as a single dose.

In the hospital setting additional doses may be given if required. Any additional doses should be given with caution and only if the potential benefits outweigh the risks. At least 20 minutes must have elapsed before the next dose.

No more than 20mg should be given in any 24-hour period.

Use of Droperidol should be short term for acute severe episodes only.

Outside the hospital setting, a single injection may 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.

For patients with acute severe mania or agitation, it is recognised that performing an ECG prior to the dose may be difficult. However, an ECG should be performed as soon as the patient's acute symptoms have subsided.

Use in renal and/or hepatic impairment.

Since Droleptan is metabolised extensively in the liver, the agent should be used with caution in patients with impaired hepatic function. Droleptan should also be used in caution with renal impairment. Lower doses are recommended in renal and/or hepatic impairment. (see section 4.4).

Use in elderly.

Elderly or frail patients or individuals with a history of adverse reactions to neuroleptic agents may require less Droleptan and half the normal dose may be sufficient for a therapeutic response.

Use in children.

Prevention and treatment of post-operative nausea and vomiting: The safety of Droleptan in children

younger than two years of age has not been established. Therefore, this agent is not recommended in this age group.

4.3 Contraindications

Droleptan is contraindicated in:

- patients with known hypersensitivity to the agent or its metabolites
- patients with severe depression
- comatose individuals
- patients with Parkinson's disease.
- phaeochromocytoma
- Droleptan 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 Warnings and Precautions).
- Droleptan is contraindicated in patients with acquired long QT interval, such as that associated with concomitant use of medicines known to prolong the QT interval known hypokalaemia or hypomagnesaemia or clinically significant bradycardia.
- Droleptan 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 Droleptan should be weighed against the potential risk. Droleptan should only be used under appropriate medical supervision.

Central nervous system

Droperidol may enhance CNS depression produced by other CNS-depressant drugs. Any patient subjected to anaesthesia and receiving potent CNS depressant agents or showing CNS depression should be monitored closely.

Concomitant use of metoclopramide and other neuroleptics may lead to an increase in extrapyramidal symptoms and should be avoided (see section 4.5).

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

Cardiovascular

Mild to moderate hypotension and occasionally (reflex) tachycardia has been observed following the administration of Droleptan. This reaction usually subsides spontaneously. However, should hypotension persist, the possibility of hypovolaemia should be considered, and appropriate fluid replacement administered.

Cardiac arrythmias, QT prolongation and torsade de pointes have been reported with Droleptan (see section 4.8). ECG monitoring and full cardiac resuscitation facilities should be available and patients who may be at a higher risk appropriately monitored.

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

- 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 ventricular arrhythmia and should continue for 30 minutes following single I.V. administration. The requirement for continuous ECG monitoring should be considered by the physician depending on the individual patient.

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.

Patients with a history of alcohol abuse, or recent high intakes are at the risk of increased arrhythmia and should be thoroughly assessed before Droleptan is administered.

To reduce risks relating to QT prolongation, caution is necessary in patients taking medicinal products likely to induce electrolyte imbalance (hypokalaemia and/or hypomagnesaemia) e.g. potassium-wasting diuretics, laxatives, and glucocorticoids, and use with other medicines that may cause bradycardia (see also section 4.3, 4.5).

General

In patients with diagnosed or suspected pheochromocytoma, severe hyper-tension and tachycardia have been observed after administration of Droleptan. Therefore, the use of Droleptan should be avoided in such patients. (See section 4.3).

Droleptan is contraindicated in patients suffering from severe depression or Parkinson's disease. (See section 4.3).

In case of unexplained hyperthermia, it is essential to discontinue treatment, since this sign may be one of the elements of malignant syndrome reported with neuroleptics.

Substances inhibiting the activity of cytochrome P450 iso-enzymes (CYP) CYP1A2, CYP3A4 or both could decrease the rate at which Droperidol is metabolised and prolong its pharmacological action. Caution is advised if Droleptan 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. Droleptan should be used with caution in patients with risk factors for stroke.

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.

4.5 Interaction with other medicines and other forms of interaction

Medicines known to prolong the QT interval are contraindicated with Droleptan. 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); certain antihistamines (such as astemizole and terfenadine); cisapride, bepridil, halofantrine and sparfloxacin.

Droleptan 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, Droleptan may potentiate respiratory depression caused by opioids.

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

Concomitant use of Droleptan with CYP1A2 inhibitors and/or CYP3A4 inhibitors could decrease the rate of Droleptan 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.

Concomitant use of medicinal products that induce extrapyramidal symptoms, e.g. metoclopramide and other neuroleptics, may lead to an increased incidence of these symptoms and should therefore be avoided.

To prevent QT prolongation, caution is necessary when patients are taking medicinal products likely to induce electrolyte imbalance (hypokalaemia and/or hypomagnesaemia) e.g. potassium-wasting diuretics, laxatives, and glucocorticoids. In addition, if other medicines are taken that may cause bradycardia.

Substances inhibiting the activity of cytochrome P450 iso-enzymes (CYP) CYP1A2, CYP3A4 or both could decrease the rate at which Droleptan is metabolised and prolong its pharmacological action. Hence, caution is advised if Droleptan is given concomitantly with CYP1A2 inhibitors, CYP3A4 inhibitors or both.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Category C

Neonates exposed to antipsychotic drugs (including Droleptan) 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.

Droleptan 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 Droleptan in these situations should be carefully weighed against the possible hazards.

Breastfeeding

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

4.7 Effects on ability to drive and use machines.

Droperidol has major influence on the ability to drive and use machines.

Patients should only drive or operate a machine if sufficient time has elapsed after the administration of Droleptan, i.e. about 24 hours and they are not experiencing any lasting sedation or other effects.

4.8 Undesirable effects

System Organ Class	**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)
Blood and lymphatic systems disorders				Blood dyscrasias	
Immune system disorders			Anaphylactic reaction; Angioneurotic oedema; Hyper-sensitivity		
Metabolism and nutrition disorders					Inappropriate anti-diuretic hormone secretion
Psychiatric disorders		Anxiety; Restlessness/Akathisia;	Confusional states; Agitation	Dysphoria	Hallucinations
Nervous system disorders	Drowsiness	Dystonia; Oculogyration		Extrapyramidal disorder; Convulsions; Tremor	Epileptic fits; Parkinson's disease; Psychomotor hyperactivity; Coma
Cardiac disorders		Tachycardia; Dizziness	Cardiac arrhythmias, including ventricular arrhythmias	Cardiac arrest; *Torsades de pointes ;* Electrogram QT prolonged	
Vascular disorders	Hypotension				Syncope
Respiratory, thoracic and mediastinal disorders					Bronchospasm; Laryngospasm
Skin and subcutaneous system disorders			Rash		
General disorders and administration site conditions			Neuroleptic malignant syndrome (NMS)	Sudden death	

The most frequently reported events during clinical experience are incidents of drowsiness and sedation. In addition, less frequent reports of hypotension, cardiac arrhythmias, neuroleptic malignant syndrome (NMS) and symptoms associated with NMS, plus movement disorders, such as dyskinesias, plus incidents of anxiety or agitation have occurred.

CNS Effects

Droleptan 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, Droleptan 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, Droleptan 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 has been observed following administration of Droperidol (see WARNINGS AND PRECAUTIONS). Should hypotension persist, the possibility of hypovolaemia 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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms

The manifestations of Droleptan 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 Droleptan. 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

Droleptan is a butyrophenone neuroleptic agent. Its pharmacological profile is characterised mainly by dopamine-blocking and α1-adrenolytic effects. Droleptan 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.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Droleptan solution for injection - 2.5 mg/mL contains Lactic acid, mannitol, and water for injection q.s.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from date of manufacture.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Droleptan Droperidol injection - 2.5 mg in 1 mL brown glass ampoules in cartons of 10

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
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Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

28 August 2023

SUMMARY TABLE OF CHANGES

Date	**Section(s) Changed**	**Change (s)**
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.
September 2019	4.4	Safety update to include precautions for use in sleep apnoea

August 2023	Section 4.1, 4.2, 4.3,4.4, 4.5,4.6, 4.7 and 4.8	Safety update
December 2023	Section 4.8 and 4.9	Reformat consistent with new Medsafe Data Sheet Template-