Applicant: MC Pharma (Pty) Ltd

Product name: Inapsin

Dosage form: Solution for injection

Strength: 2,5 mg/ml

06 March 2025

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1 NAME OF THE MEDICINE

INAPSIN® 2.5 mg/ml injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains droperidol 2,5 mg.

Excipient with known effect:

Sodium < 23 mg per ml

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear colourless solution in 2 ml glass ampoules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Provided certain precautions are taken (see sections 4.2, 4.3, 4.4, 4.8). INAPSIN® is indicated for the reduction in the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients for whom other treatments are ineffective or inappropriate.

4.2 Posology and method of administration

Posology

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

INAPSIN® can be administered to both adults and children. The following dosage regimen is recommended:

Adult dosage: The maximum recommended initial dose is 2,5 mg IM or slow IV. Additional 1,25 mg amounts may be administered with caution only if the potential benefit outweighs the potential risk.

Special populations

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

Paediatric populations

For children 2 to 12 years: The maximum recommended initial dose is 0,1 mg/kg body mass taking into account the patient's age and other clinical factors. However, additional doses should be administered with caution and only if the potential benefit outweighs the potential risk.

Safety in children under the age of 2 years has not been established.

Vital signs and ECG 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 or diagnostic procedure and subsequently for a period consistent with best medical judgement, but at least 7 hours after the end of the procedure (see section 4.8, 4.4 and 4.3).

NOTE: When INAPSIN® is used in certain procedures, such as bronchoscopy, appropriate topical anaesthesia is still necessary. (Refer to section 4.4).

Method of administration

Intramuscular or slow Intravenous injection

4.3 CONTRAINDICATIONS

- INAPSIN® is contraindicated:
  - in patients with a known hypersensitivity to the medicine or its metabolites. (Refer section 6.1).
  - Hypersensitivity to butyrophenones.
  - in severely depressed patients,
  - in patients with Parkinson's disease,
  - Hypokalaemia or hypomagnesaemia;
  - Bradycardia (< 55 heartbeats per minute);
  - Known concomitant treatment leading to bradycardia;
  - Phaeochromocytoma and
  - in comatose individuals.
- Inapsin is contraindicated in patients with known or suspected prolonged QT interval (QTc of > 450 msec in females and > 440 msec in males). This includes patients with congenitally long QT interval, patients who have a family history of congenital QT prolongation

andpatients treated concomitantly with medicinal products known to have a risk of torsades de pointes through QT prolongation (see section 4.5).

- Safety in children under 2 years has not been established.
- INAPSIN® is not recommended for any use other than for the treatment of post-operative nausea and vomiting in patients for whom other treatments are ineffective or inappropriate (see sections 4.1 and 4.4).

4.4 Special warnings and precautions for use

- Fluids and other countermeasures to manage hypotension should be readily available.
- Since INAPSIN® is metabolised extensively in the liver, the medicine should be used with caution in patients with impaired hepatic function.
- Sedation and impairment of alertness may occur particularly with higher doses and at the start of treatment and may be potentiated by alcohol. Patients should only drive or operate machinery after 24 hours has elapsed after the administration of INAPSIN® (See section 4.7).
- In patients with diagnosed or suspected pheochromocytoma, severe hypertension and tachycardia have been observed after administration of droperidol. Therefore, the use of droperidol should be avoided in such patients. **[Cases of QT prolongation and/or torsade's de pointes have been reported in patients receiving INAPSIN® at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal. INAPSIN® should therefore be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the ability to achieve an effective dose due to intolerable adverse effects from those medicines (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CONTRAINDICATIONS). All patients should undergo a 12-lead ECG**

before administration of INAPSIN® to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, INAPSIN® should NOT be administered.]

- For patients in whom the potential benefit of INAPSIN® treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for a period consistent with medical judgement, but at least 7 hours after the end of the procedure. INAPSIN® is contraindicated in patients with known or suspected QT prolongation, including patients with congenital QT syndrome.
- INAPSIN® should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g. congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalaemia, hypomagnesemia, or administration of other medicines known to increase the QT interval).
- Other risk factors may include age over 65 years, alcohol abuse, and use of medicines such as benzodiazepines, volatile anaesthetics, and IV opiates.
- Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.
- Injectable droperidol prolongs the QT interval in a dose-dependent manner.
- Patients with, or suspected of having, the following risk factors for cardiac arrhythmia should be carefully evaluated before 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, ischemic heart disease), family history of sudden death, renal failure (particularly when on chronic dialysis), significant chronic obstructive pulmonary disease and respiratory failure, risk factors for electrolyte disturbances as seen in patients taking potassium-wasting diuretics, in association with the administration of insulin in acute settings or in patients with prolonged vomiting and/or

diarrhoea. In these patients INAPSIN® should be used with extreme caution and an ECG, an assessment of serum electrolytes (potassium and magnesium) and renal function should be performed as part of this evaluation.

- Any patient subjected to anaesthesia and receiving potent central nervous system depressant medicines or showing central nervous system depression should be closely monitored.
- Mild to moderate hypotension and occasionally (reflex) tachycardia have been observed following administration of INAPSIN®. This reaction usually subsides spontaneously. However, should hypotension persist, the possibility of hypovolaemia should be considered, and appropriate fluid replacement administered.
- Tardive dyskinesia: Tardive dyskinesia may appear in some patients on long-term therapy or may appear after therapy, has been discontinued. The syndrome is characterised by rhythmical involuntary 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 dosage is increased or when a switch is made to a different antipsychotic medicine. Treatment should be discontinued as soon as possible.
- Neuroleptic malignant syndrome (NMS): INAPSIN® has been associated with exceptional cases of NMS, a seldom idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability and altered consciousness. Hyperthermia is often an early sign of this syndrome.
- Anti-psychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.
- INAPSIN® must be used with extreme caution in patients receiving lithium.
- INAPSIN® should be used with caution in patients with liver and kidney dysfunction.

- Severe dystonic reactions have followed the use of INAPSIN®; it should therefore be used with extreme care in susceptible patients, such as children, adolescents and the elderly.

4.5 Interaction with other medicines and other forms of interaction

- Concomitant use with metoclopramide and other neuroleptics may induce extrapyramidal symptoms, therefore should be avoided.
- Medicines known to prolong the QT interval are contraindicated (refer to section 4.3). Examples include certain antiarrhythmics, such as those of Class A (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, haloperidol, risperidone, pimozide and sertindole); certain antihistamines (such as astemizole and terfenadine); cisapride, bepridil, halofantrine and sparfloxacin. Please note that this list is not exhaustive.
- INAPSIN® may potentiate the action of sedative medicines (barbiturates, benzodiazepines, morphinomimetics). The same applies to antihypertensive medicines eg. methyldopa, so that orthostatic hypotension may ensue.
- INAPSIN® may potentiate respiratory depression caused by opioids.
- INAPSIN® must be administered in reduced dosage (as low as ½ the dosage usually recommended) when other central nervous system depressants are prescribed concomitantly to avoid the possibility of potentiation.
- Since INAPSIN® blocks dopamine receptors, it may inhibit the action of dopamine agonists, such as bromocriptine, lisuride and of l-dopa. The dosage of anti-convulsants may need to be increased to take account of the lowered seizure threshold.

- Theoretically, certain medicines (eg. phenobarbital, carbamazepine, phenytoin), as well as smoking and alcohol consumption, which may stimulate metabolising enzymes in the liver, may enhance the metabolic breakdown of neuroleptics, possibly necessitating adjustment of the dose.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females.

No information available.

Pregnancy

Safety in pregnancy has not been established.

Droperidol is not teratogenic in animals and has been used in a few isolated instances in pregnant women.

Breastfeeding

Butyrophenones are excreted in breast milk. If the use of INAPSIN® is essential, breastfeeding should be avoided.

Fertility

No fertility data is available.

4.7 Effects on ability to drive and use machines

Patients should only drive or operate machinery after 24 hours has elapsed after the administration of INAPSIN® as sedation and impairment of alertness may occur particularly with higher doses and at the start of treatment and may be potentiated by alcohol. (See section 4.4).

4.8 Undesirable effects

a) Summary of the safety profile

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.

Symptoms potentially associated with NMS have occasionally been reported i.e. changes in body temperature, stiffness and fever. An alteration in mental status with confusion or agitation and altered consciousness, have been seen. Autonomic instability may manifest as tachycardia, fluctuating blood pressure, excessive sweating/salivation and tremor. In extreme cases NMS may lead to coma, or renal and/or hepato-biliary problems.

Isolated cases of amenorrhoea, galactorrhoea, gynaecomastia, hyperprolactinaemia, and oligomenorrhoea have been associated with prolonged exposure in psychiatric indications.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic medicinal products - frequency unknown.

b) Tabulated list of adverse reactions

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				Blood dyscrasias	
Immune system disorders			Anaphylac-Tic reaction, Angioneu-		

			rotic oedema, Hypersen-sitivity		
Metabolism and Nutrition Disorder					**Inapprorpiate antiduiretic hormone secretion**
Psyciatric disorders		**Anxiety; Restlessnes Akathisia**	**Confusional states; Agitation**	**Disphoria**	**Hallucinations**
Nerves system disorders	**Drowsiness**				
Cardiac disorders	**Tachycardia; dizziness**	**Cardiac Arythmiass; Ventricular Arythmiass**	**Cardiac Arrest; Torsade de points; Electrogram QT prolonged**		
Vascular Disorders	**Hypotension**				**Syncope**
Respiratory; thoracic and mediastinal disorders					**Bronchospasm and Laryngo spasm**
Skin and subcutaneous system disorders			**Rash**		
General disorders and administration site conditions			**Neuroleptic Malignant Syndrome (NMS)**	**Sudden Death**	

c. Description of selected adverse reactions`

INAPSIN® may produce symptoms potentially associated with NMS have occasionally been reported i.e. changes in body temperature, stiffnessand fever. An alteration in mental status with confusion or agitation and altered consciousness, have been seen. Autonomic instability may manifest as tachycardia, fluctuating blood pressure, excessive sweating/salivation and tremor.In extreme cases NMS may lead to coma, or renal and/or hepato-biliary problems.

Isolated cases of amenorrhoea, galactorrhoea, gynaecomastia, hyperprolactinaemia, and oligomenorrhoea have beenassociated with prolonged exposure in psychiatric indications.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis havebeen reported with antipsychotic medicinal products - frequency unknown.

INAPSIN® may produce Parkinsonian or dyskinetic extrapyramidal side effects (dystonia, akathisia, oculogyric crisis). These are readily and completely reversible by treatment with an anti-Parkinsonian medicine of the anticholinergic type.

Cases of QT-interval prolongation, ventricular arrhythmia and sudden death have been reported less frequently. They may occur more frequently with high doses and in predisposed patients. Some cases have occurred in patients with no known risk factors and at doses at or below recommended doses (see Warnings and Precautions).

4.9 Overdose

Symptoms

The manifestations of INAPSIN® overdosage are an extension of its pharmacological actions (see Section 5). Symptoms of accidental overdosage are psychic indifference with a transition to sleep, sometimes in association with lowered blood pressure. Cardiac arrhythmias may occur. At higher doses, extrapyramidal disorders may occur (salivation, abnormal movements, and sometimes muscle rigidity). Convulsions may occur at toxic doses. Cases of QT-interval prolongation, ventricular arrhythmias and sudden death have been reported in overdoses.

Treatment

No specific antidote is known. However, when extrapyramidal reactions occur, an anticholinergic should be administered. As with any patients receiving INAPSIN® therapeutically (see Section 4.2 i.e. Cardiac Monitoring, 4.4 and 4.8), it is recommended that any patient who has taken an overdose of INAPSIN® be administered an ECG immediately. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

INAPSIN® is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine blocking and α_1-adrenolytic effects. INAPSIN® is devoid of anticholinergic and antihistaminic effects. It has a marked tranquillizing and sedative effect, alleviates apprehension and causes a state of mental detachment and indifference while maintaining a state of reflex alertness INAPSIN® produces an antiemetic effect. It lowers the incidence of nausea and vomiting during surgical procedures and provides antiemetic protection in the post-operative period INAPSIN® potentiates other central nervous system depressants. It induces mild α_1-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 arrythmia, but it does not prevent other forms of cardiac arrythmia.

Paediatric population

Safety not proven for children younger than 18 Years.

5.2 Pharmacokinetic properties

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

Distribution

Following intravenous administration, plasma concentrations fall rapidly during the first 15 minutes. Plasma protein binding amounts to 85 – 90 %. The distribution volume is 99 – 168 litres.

Metabolism

Droperidol is extensively metabolised in the liver, and undergoes oxidation, dealkylation, demethylation andhydroxylation by cytochrome P450 isoenzymes 1A2 and 3A4, and to a lesser extent by 2C 19. The metabolites aredevoid of neuroleptic activity.

Elimination

Elimination occurs mainly through metabolism; 75% is excreted via the kidneys. Only 1% of the active substance isexcreted unchanged with urine, and 11% with faeces. Plasma clearance is 0.8 (0.4 - 1.8) l/min. The elimination half-life(t1/2ß) is 134 ± 13 min.

Drug Interactions

A study combining ondansetron (4 mg) and droperidol (1 mg) showed that when administered together there was nopharmacokinetic interaction between the two drugs.

Paediatric Population

In a study of 12 children (age 3.5 to 12 years), the values for distribution volume and clearance reported were lowerthan those found in the adult population (0.58 ± 0.29 l/kg and 4.66 2.28 ml/kg*min respectively) and decrease inparallel. The elimination half-life (101.5 ± 26.4 min) was similar to that found in adults.

5.3 Preclinical safety data

No information is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- D-Mannitol
- Dihydroxy-butanedoic acid
- Water for injection

6.2 Incompatibilities

No information is available

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 °C. Protect from light.

6.5 Nature and contents of container

INAPSIN® injection is supplied in 2 ml brown glass ampoules, packed in boxes of 5, 10 and 30 ampoules.

6.6 Special precautions for disposal and other handling

INAPSIN® 2,5 mg/ml injection is a clear, colourless solution, however, as a precautionary measure, it is recommended that an in-line filter is used.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

B/2.6.5/1012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/12/1987 date on registration certificate

10 DATE OF REVISION OF THE TEXT

06 March 2025.