

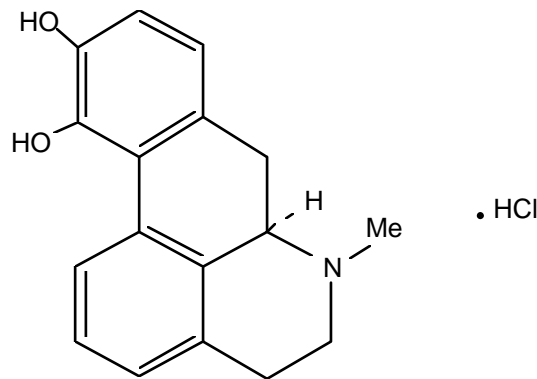
APOMINE™ INJECTION

NAME

Apomine™ Injection

DESCRIPTION

Apomine™ Injection is a sterile solution containing 10 mg/mL of apomorphine hydrochloride in Water for Injections B.P. Sodium metabisulfite 1 mg/mL is included in the formulation as an antioxidant. The pH of the injection is 3.0 to 4.0. The CAS registry number of apomorphine hydrochloride, anhydrous is 41372-20-7 and the chemical structure is shown below:



PHARMACOLOGY

Apomorphine is a directly acting dopamine receptor agonist, structurally related to dopamine. Apomorphine has high in vitro binding affinity for the dopamine D₄ and D₅ receptor (K_i : 4 and 14 nM respectively), moderate affinity (K_i : 26 to 130 nM) for the dopamine D₂ and D₃, adrenergic α_{1D} , α_{2B} , α_{2C} receptors, serotonin 5HT_{1A}, 5HT_{2A}, 5HT_{2B}, and 5HT_{2C} receptors and low affinity for the dopamine D₁ receptor (K_i : 370 nM). Apomorphine exhibits no affinity for the adrenergic β_1 and β_2 or histamine H₁ receptors.

The effect of apomorphine as an antiparkinsonian agent is believed to be the result of direct stimulation of postsynaptic D₂ dopamine receptors, but stimulation of presynaptic D₂ dopamine receptors and antagonism of α_2 adrenergic receptors may also be important. Apomorphine reduces the tremor, rigidity and bradykinesia in patients receiving levodopa. Apomorphine induces vomiting by direct stimulation of the medullary chemoreceptor trigger zone.

The peripheral pharmacokinetics of apomorphine have been studied following subcutaneous injection, subcutaneous infusion and intravenous infusion. The peak plasma concentration occurs as early as three minutes following subcutaneous bolus injection.

The distribution half-life was found to be five minutes while the elimination half-life ($t_{1/2}$) was found to be 33 minutes. The volume of distribution, plasma clearance and half life were similar for subcutaneous injection, subcutaneous infusion and intravenous infusion. The rapid and complete absorption from subcutaneous tissues and rapid clearance is believed to correlate with the rapid onset and brief duration of action respectively. Antiparkinsonian effects are observed within five minutes following subcutaneous bolus administration.

Apomorphine reaches a concentration in the brain which is up to eight times higher than that in plasma, due to high lipid solubility which allows rapid equilibration between blood and tissue compartments. Following intramuscular or subcutaneous administration apomorphine is reported to be well absorbed, and to be metabolised in the liver. Routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation to norapomorphine by CYP 2B6, CYP 2C8

and CYP 3A4. The major metabolite in humans after sublingual administration was apomorphine sulphate.

INDICATIONS

Apomine™ Injection is indicated to reduce the number and severity of 'off' phases in patients with Parkinson's Disease severely disabled by motor fluctuations refractory to conventional therapy. Initiation of therapy with Apomine™ Injection should be undertaken in a specialist unit in a hospital setting. Conventional therapy should be continued during 'on' phases.

CONTRAINDICATIONS

Apomine™ Injection is contraindicated in patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically-related products. Apomine™ Injection should not be administered to patients with pre-existing neuropsychiatric problems or dementias due to either pathological processes, eg. Alzheimer's disease, or to patients whose 'on' response to l-dopa is marred by severe dyskinesia, hypotonia or psychotoxicity. Apomine™ Injection is also contraindicated in patients with inadequate renal or liver function, unstable coronary vascular disease, cerebrovascular disease, respiratory depression or CNS depression.

Apomine™ Injection is also contraindicated in patients with a known hypersensitivity to sodium metabisulfite.

PRECAUTIONS

For Subcutaneous Use Only (see Adverse Effects).

Patients sensitive to morphine or its derivatives may be sensitive to Apomine™ Injection. Apomine™ Injection should therefore not be administered to patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically-related compounds (See Contraindications).

Apomine™ Injection contains sodium metabisulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people.

In patients with cardiac decompensation or cerebrovascular disease, vomiting may cause an increase in blood pressure that may lead to haemorrhage and vascular accidents. Apomine™ Injection is therefore contraindicated in these patients (See Contraindications).

Caution should be used in administering Apomine™ Injection to patients with a predisposition to nausea and vomiting. Apomine™ Injection may cause an increased risk of persistent vomiting. A risk-benefit assessment should be considered in these patients.

Caution is also recommended in debilitated or geriatric patients, since they may show an increased susceptibility or be more sensitive to the respiratory depressant effects of Apomine™ Injection.

Since apomorphine, especially at high doses, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for Torsades de pointes arrhythmia.

Compulsive behaviour

Compulsive behaviour such as gambling, hyper sexuality, shopping, eating, medication use and punding (repetitive purposeless activity) has been reported in patients taking dopamine agonists for Parkinson's disease, especially at high doses (See Adverse Effects). Prescribers, patients and care givers should be alert to the possibility of such behaviour, which may have serious financial and social consequences. Health care professionals should inform patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual.

Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment

with apomorphine. Patients who have experienced somnolence must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

Apomine™ Injection should be used with caution in patients with endocrine, renal, pulmonary or cardiovascular disease.

Periodic evaluation of hepatic, haemopoietic, renal and cardiovascular function is advised.

Patients with severe renal insufficiency may require the dosing interval for domperidone to be less frequent, see Dosage and Administration - Pretreatment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients being treated with apomorphine and presenting with somnolence must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) unless patients have overcome such experiences of somnolence (see above).

EFFECTS ON FERTILITY

In a fertility study in male rats, fertility was decreased at 2 mg/kg/day s.c., one tenth that of the maximum recommended human dose (based on body surface area). Effects on female fertility have not been determined."

USE IN PREGNANCY

Category B3. The safety of using Apomine™ Injection during pregnancy has not been established in either human or animal studies. Apomine™ Injection should therefore not be used in pregnant women, or those likely to become pregnant.

USE IN LACTATION

It is not known whether Apomine™ Injection is excreted in breast milk although problems in humans have not been documented. Nevertheless, because many drugs are excreted in human milk and because of the potential for serious adverse drug reactions due to apomorphine in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the drug to the mother.

CARCINOGENICITY

No carcinogenicity studies have been performed.

GENOTOXICITY

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. Apomorphine was not genotoxic *in vivo* in a mouse micronucleus test or in a rat unscheduled DNA synthesis test.

INTERACTIONS WITH OTHER DRUGS

Drugs which interfere with central amine mechanisms such as tetrabenazine, metoclopramide, antipsychotic dopamine-blocking agents (such as phenothiazines, thioxanthenes and butyrophenones), amphetamines and papaverine should be avoided. If their administration is considered essential, extreme care should be taken and the patient monitored for signs of potentiation, antagonism or other interactions and for any unusual adverse effects.

Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of antihypertensive and cardiac active medicinal products.

There is a potential interaction between clozapine and apomorphine.

It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

The possible side effects of apomorphine on the plasma concentrations of other medicinal products have not yet been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

ADVERSE EFFECTS

Gastrointestinal side effects including nausea and vomiting appear to be the most prevalent adverse effect, however tolerance to these effects develops rapidly. Pretreatment with domperidone may reduce or prevent these effects. Apomorphine is associated with somnolence. Drowsiness and sedation occur in most patients on initial treatment but these effects largely subside with repeated dosing, although in some patients these effects may persist. Tachyphylaxis to postural related faintness or syncope also occurs rapidly. Increasingly severe on-phase dyskinesias may be associated with the use of Apomine™ Injection. They may be dose-limiting and have the potential to mar the therapeutic response in some patients.

Itchy nodular lesions at the injection site may be severe in patients on continuous subcutaneous infusions of Apomine™ Injection, but usually disappear within 48 hours in patients receiving intermittent injections. Local bruising, fibrosis and skin necrosis have been reported.

Peripheral blood eosinophilia, elevated by up to 10%, has occurred in patients on continuous subcutaneous infusion of apomorphine. Blood counts returned to normal in about half of the patients who received treatment over one year.

The use of Apomine™ Injection in conjunction with levodopa treatment may cause Coombs' positive haemolytic anaemia. An initial screen prior to commencement of treatment and at 6 monthly intervals is recommended. In the event of the development of a haemolytic anaemia, a haematological specialist should be consulted. The dose of Apomine™ Injection and/or levodopa should be reduced, with careful monitoring of the patient's motor state. It may be necessary to discontinue treatment with levodopa and/or Apomine™ Injection in the event that it is not possible to control the anaemia satisfactorily.

Compulsive behaviour such as gambling, hyper sexuality, shopping, eating, medication use and punding (repetitive, purposeless activity) has been reported in patients taking dopamine agonists for the treatment of Parkinson's disease, especially at high doses (see Precautions).

Other adverse reactions to apomorphine that have been reported infrequently include visual hallucinations and hallucinations, somatitis, confusion, transient rises in serum prolactin, transient metallic taste, spontaneous penile erection, rhinorrhoea, increased lacrimation, reduced facial hair growth and loss of libido.

DOSAGE AND ADMINISTRATION

The optimal dosage of Apomine™ Injection has to be determined on an individual patient basis. Hospital admission under appropriate specialist supervision is advised when establishing a patient's therapeutic regime.

It is essential that the patient is established on the antiemetic domperidone for at least 48 – 72 hours prior to initiation of therapy.

PATIENT SELECTION: For patients in whom conventional therapy has failed Apomine™ injections are only considered to be suitable for Parkinson's disease patients capable of recognising and anticipating 'off' phases in motor performance. Patients must be capable and motivated for Apomine™ Injection to be used effectively. Adult patients through all age ranges have been successfully managed with apomorphine injections. Apomine™ Injection is not recommended in children and adolescents up to 18 years of age.

Elderly patients, in appropriate circumstances, can be successfully managed with Apomine™ Injection.

The practical steps described below should be followed when commencing a patient on treatment:

- Pre-treat with domperidone.
- Discontinue all existing antiparkinsonian medication to provoke an 'off' phase in motor performance.
- Determine the threshold dose response to Apomine™ Injection that produces an unequivocal motor response.
- Re-establish other antiparkinsonian agents.
- Determine effective treatment regimen for Apomine™ Injection.
- Teach patient and/or carer how and when to administer.
- Discharge from hospital.
- Monitor frequently and adjust dosage regimen as appropriate.
- Full details are given below.

PRE-TREATMENT: Domperidone is a peripherally acting dopamine receptor antagonist given by mouth to prevent nausea and vomiting. Domperidone is commenced 48 - 72 hours prior to the first dose of Apomine™ Injection. When patients are stabilised with respect to dosage of Apomine™ Injection, the dose of domperidone is reduced by 10 mg per day every week until mild nausea appears. The maintenance dose of domperidone is the lowest level which completely prevents nausea. Domperidone can usually be withdrawn after several weeks. Patients with severe renal insufficiency will require the dosing interval of domperidone to be changed from three times a day to once or twice a day. For further information regarding domperidone refer to the product information and consumer product information.

PROVOKING AND ASSESSING AN 'OFF' PHASE: After at least 3 days of hospitalisation all anti-parkinsonian therapy is withheld overnight to provoke an 'off' phase in motor performance and to undertake a baseline motor assessment as follows:

- (a) Alternate, unilateral hand-tapping for 30 seconds on mounted digital counters (preferably 20 cm apart) (Ref. Hughes, AJ et al., *Lancet*, 1990; 336:32-34).
- (b) Time taken to walk 12 metres.
- (c) Clinical assessment of tremor and dyskinesia according to a four point scale (0=nil, 1=mild, 2=moderate, 3=severe).
- (d) Scoring on a modified Webster disability scale to assess 12 features of parkinsonism (maximum disability score of 36) (Ref. Kempster, PA et al., *J Neurol Neurosurg Psychiatry*, 1989; 52:718-23).

DETERMINATION OF THE THRESHOLD DOSE: Following baseline motor assessment the patient is challenged for Apomine™ Injection responsiveness according to the following schedule:

- 1.5 mg Apomine™ Injection (0.15 mL) is injected subcutaneously and the patient is observed over 30 minutes for motor responsiveness.
- If no or poor response is obtained, a second dose of 3 mg Apomine™ Injection (0.3 mL) is given 40 minutes after the first dose, and the patient observed for a further 30 minutes.
- The dosage is increased in an incremental fashion every 40 minutes and the patient observed carefully for an unequivocal motor response. The third dose is 5 mg s.c., and the fourth dose is 7 mg s.c. If the patient shows no response to the 7 mg dose then the patient must be classified as a non-responder to Apomine™ Injection and no further attempts to provoke a motor response should be made. If the patient shows only a mild response to the 7 mg dose, a maximum dose of 10 mg can be used to see if an unequivocal motor response is possible.
- The lowest dose producing an unequivocal motor response is called the threshold dose. For the majority of patients the threshold dose is less than 7 mg Apomine™ Injection (0.7 mL), although very occasionally it can be up to 10 mg Apomine™ (1.0 mL).

Motor responsiveness is judged to be positive if 2 or more of the following are seen:

- (a) More than 15% increase in tapping score.
- (b) More than 25% improvement in walking time.
- (c) An improvement of at least 2 points of tremor score.
- (d) An improvement of Webster's score of 3 or more.

INITIATION OF TREATMENT: Following establishment of an acceptable threshold dose of Apomine™ Injection, the patient should be restarted on conventional antiparkinsonian therapy.

A subcutaneous injection of the established threshold dose may then be given into the lower abdomen or outer thigh at the first signs of an 'off' phase. The patient should then be observed over the following hour and the quality of their 'on' phase noted. It may be appropriate to modify the dose of Apomine™ Injection according to the patient's response.

Close monitoring of therapeutic benefits and adverse reactions under specialist supervision is required after initiation of treatment.

Apomine™ Injection is administered by the subcutaneous route, either by intermittent injection or continuous infusion. Intermittent injection is either into the anterior abdominal wall or anterolateral thigh via a disposable 1 mL insulin syringe. The usual dosage range is 2.4 - 3.6 mg per injection; the maximum single dose being 6 mg and the maximum total daily dose being 50 mg.

Correct dosage is assured by mounting the filled syringe in a Penject dose metering device. The intermittent injection is given in an undiluted form. For microbiological reasons, the contents of a pre-filled syringe used for intermittent injections should be used within 24 hours of filling. Store in a refrigerator at 2 - 8 degrees C between injections. Any solution remaining at the end of the day should be discarded and not reused on the following day.

Patients who have shown a good 'on' phase response during the initiation stage, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (e.g. 8 - 10 injections per day), may be commenced on or transferred to continuous subcutaneous infusion by minipump.

Continuous subcutaneous infusion of Apomine™ Injection is effected via administration by portable syringe driven pump at a minimum dilution of 1:1 with Sodium Chloride 0.9% (Normal Saline). The dose should be titrated to the patient's response. Infusion rates can be commenced at 1 mg/hr, and then increased as necessary. The maximum daily dose should in general not exceed 200 mg/day. In clinical studies the required infusion rate varies between 1.25 and 5.5 mg/hr (equivalent to 0.02 and 0.08 mg/kg/hr), with most patients requiring (a total of) between 2 and 4 mg/hr.

Infusions should be run for waking hours only. Unless the patient is experiencing night time problems 24 hour infusions are not advised. The infusion site should be changed every 12 hours. Prolonged infusion times are associated with local adverse effects to a more severe degree.

MONITORING TREATMENT: Long-term specialist supervision of patients is advised.

There is a high probability of adverse effects to Apomine™ Injection therapy. The frequency and severity of adverse events should be monitored carefully at regular intervals and a reassessment of the patient carried out if appropriate. Adjustments to the dosage or discontinuation may be necessary.

OVERDOSAGE

The clinical features of overdose of Apomine™ Injection are an extension of the pharmacological effects of the drug. They include nausea and persistent vomiting, dyskinesias, hypotension and acute circulatory failure, cardiac arrest, respiratory depression, drowsiness and central nervous system depression or stimulation, euphoria, restlessness and hallucinations and possibly coma and death. Concomitant use of domperidone may exacerbate the clinical features of overdose.

An opioid antagonist such as naloxone may be given to treat excessive vomiting, central nervous system depression and respiratory depression due to Apomine™ Injection overdose. Excessive vomiting may also be treated with domperidone. Atropine may be also used to treat bradycardia. To treat hypotension, appropriate measures should be taken.

In case of overdose, immediately contact the Poisons Information Centre for advice (in Australia, call 13 11 26; in New Zealand call 0800 764 766).

STORAGE

Store the 1 mL ampoules at 2 - 8°C (Refrigerate. Do not freeze). Protect from light.

Store the 2 mL and 5 mL ampoules below 25°C (Do not freeze). Protect from light.

PRESENTATION

<u>Strength</u>	<u>Pack</u>
10 mg/1 mL	5 x 1 mL ampoule
20 mg/2 mL	5 x 2 mL ampoule
50 mg/5 mL	5 x 5 mL ampoule

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