Apomine™ Solution for Infusion

NAME OF THE MEDICINE
Apomorphine hydrochloride

The CAS registry number of apomorphine hydrochloride hemihydrate, is 41372-20-7 and the chemical structure is shown below:

![Chemical structure of apomorphine hydrochloride](image)

DESCRIPTION
Apomine™ Solution for Infusion for subcutaneous (SC) infusion is a clear and colourless to slightly yellow solution, free from visible particles sterile solution containing apomorphine hydrochloride in Water for Injections. Sodium metabisulfite 1 mg/mL is included in the formulation as an antioxidant. The pH of the injection is 3.0 to 4.0.

Each 20 mL vial contains 100 mg apomorphine hydrochloride, hence 1 mL of solution contains 5 mg apomorphine hydrochloride (5 mg/mL).

This product does not require dilution prior to administration.

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 (Kᵢ: 4 and 14 nM respectively), moderate affinity (Kᵢ: 26 to 130 nM) for the dopamine D₂ and D₃, adrenergic α₁D, α₂B, α₂C receptors, serotonin 5-HT₁A, 5-HT₂A, 5-HT₂B, and 5-HT₃C receptors and low affinity for the dopamine D₁ receptor (Kᵢ: 370 nM). Apomorphine exhibits no affinity for the adrenergic β₁ and β₂ 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 α₂ 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.
PHARMACOKINETICS
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 (t½) 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. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and that the brief duration of clinical action of the active substance (about 1 hour) is explained by its rapid clearance. Antiparkinsonian effects are observed within 5 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™ Solution for Infusion 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 apomorphine should be undertaken in a specialist unit in a hospital setting. Conventional therapy should be continued during ‘on’ phases.

CONTRAINDICATIONS
Apomorphine is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, morphine or chemically related products. Apomorphine should not be administered to patients with pre-existing neuropsychiatric problems, or dementias due to either pathological processes, e.g. Alzheimer’s disease, or to patients whose ‘on’ response to L-dopa is marred by severe dyskinesia, hypotonia or psychotoxicity. Apomorphine is also contraindicated in patients with inadequate renal or liver function, unstable coronary vascular disease, cerebrovascular disease, respiratory depression or CNS depression.

Apomorphine is 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 apomorphine. It should therefore not be administered to patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically related compounds (see CONTRAINDICATIONS).

Apomorphine contains sodium metabisulfite which may cause allergic type reactions, including anaphylactic symptoms and life threatening or less severe asthmatic episodes in susceptible people (see CONTRAINDICATIONS).

In patients with cardiac decompensation or cerebrovascular disease, vomiting may cause an increase in blood pressure that may lead to haemorrhage and vascular accidents. Apomorphine is therefore contraindicated in these patients (see CONTRAINDICATIONS).
Caution should be used in administering apomorphine to patients with a predisposition to nausea and vomiting. Apomorphine 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 apomorphine. Extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension.

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**
 Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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.

Apomorphine 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 fertility**
In a fertility study in male rats, fertility was decreased at 2 mg/kg/day SC, 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 B3¹
The safety of using apomorphine during pregnancy has not been established in either human or animal studies.

Apomorphine should therefore not be used in pregnant women, or those likely to become pregnant.

**Use in lactation**
It is not known whether apomorphine 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

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¹ Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects in the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage the significance of which is considered uncertain in humans.
should be made either to discontinue breastfeeding or the drug, taking into account the benefit of breast-feeding to the child and the benefit of apomorphine to the woman.

**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.

**Effects on the ability to drive and use machinery**
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 also PRECAUTIONS).

**Interactions with other Medicines**

Drugs which interfere with central amine mechanisms such as tetrabenazine, metoclopramide, antipsychotic dopamine blocking agents (such as phenothiazines, thioxanthes 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**

*Very common (>10%)*

Local induration and nodules (usually asymptomatic) often develop at subcutaneous sites of injection in most patients, particularly with continuous use. In patients on high doses of apomorphine HCl these may persist and give rise to areas of erythema, tenderness and induration. Panniculitis has been reported from these patients where a skin biopsy has been undertaken. Care should be taken to ensure that areas of ulceration do not become infected. Pruritus may occur at the site of injection.

These local subcutaneous effects can sometimes be reduced by rotation of injection sites or possibly by the use of ultrasound (if available) to areas of nodularity and induration.

*Common (1-10%)*

Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone (See DOSAGE AND ADMINISTRATION).
Transient sedation with each dose of apomorphine HCl at the start of therapy may occur; this usually resolves over the first few weeks.

Apomorphine is associated with somnolence.

Neuropsychiatric disturbances are common in parkinsonian patients. Apomorphine should be used with special caution in these patients. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine HCl therapy.

_Uncommon (0.1 – 1%)_

Postural hypotension is seen infrequently and is usually transient (See Precautions).

Apomorphine may induce dyskinesias during ‘on’ periods, which can be severe in some cases, and in a few patients may result in cessation of therapy.

Coombs’ positive haemolytic anaemia has rarely been reported in patients treated with levodopa and apomorphine. A Coombs’ test is recommended prior to commencement of treatment and as required throughout treatment. In the event of the development of a haemolytic anaemia, a haematological specialist should be consulted. The dose of apomorphine 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 apomorphine in the event that it is not possible to control the anaemia satisfactorily.

_Rare (0.01-0.1%)_

Eosinophilia has rarely occurred during treatment with apomorphine HCl.

Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur.

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine (see Precautions).

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

Thrombus formation and pulmonary embolism have occurred with central venous infusion of apomorphine. Intravenous infusion of the preparation is thus contraindicated.

**DOSAGE AND ADMINISTRATION**

The optimal dosage of Apomine™ Solution for Infusion 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.
Apomine™ Solution for Infusion (5 mg/mL) is intended for use as a continuous subcutaneous infusion with suitable pumps/syringe drivers.

**There is no need to dilute Apomine™ Solution for Infusion prior to use.**

Contains no antimicrobial agent. Apomine™ Solution for Infusion is for single use in one patient only. For microbial reasons, once opened the contents of the vial should be used for infusion immediately. The infusion site should be changed every 12 hours. Any unused solution should be discarded.

Apomine™ Solution for Infusion must not be used via the intravenous route.

**Patient selection:**
For patients in whom conventional therapy has failed, Apomine™ Solution for Infusion is only considered to be suitable for Parkinson’s disease patients capable of recognising and anticipating ‘off’ phases in motor performance. Apomine™ Solution for Infusion is not recommended in children and adolescents up to 18 years of age.

The elderly are well represented in the population of patients with Parkinson’s disease and constitute a high proportion of those studied in clinical trials of Apomorphine. The management of elderly patients treated with Apomine™ Solution for Infusion has not differed from that of younger patients, except for the extra caution on commencing therapy, because of the risk of postural hypotension.

Patients who have shown a good ‘on’ period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections, may be commenced on or transferred to continuous subcutaneous infusion by minipump and/or syringe driver.

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

- Pretreat with Domperidone.
- Discontinue all existing antiparkinsonian medication to provoke an ‘off’ phase in motor performance.
- Determine the threshold dose response to Apomine™ Solution for Infusion that produces an unequivocal motor response.
- Re-establish other antiparkinsonian agents.
- Determine effective treatment regimen for Apomine™ Solution for Infusion
- Teach patient and/or carer how and when to administer.
- Discharge from clinic or hospital.
- Monitor frequently and adjust dosage regimen as appropriate.

**Pretreatment:** 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™ Solution for Infusion. When patients are stabilised with respect to dosage of Apomine™ Solution for Infusion, the dose of domperidone is reduced by 10 mg per day every week until mild nausea appears. The maintenance dose of domperidone should be 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 domperidone Product Information.

**After provoking an ‘off’ phase in motor performance:**

**Determination of the threshold dose:**
Following baseline motor assessment, the patient is challenged for apomorphine responsiveness according to the following schedule:
• 1.5 mg apomorphine (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 apomorphine (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 SC, and the fourth dose is 7 mg SC. If the patient shows no response to the 7 mg dose then the patient must be classified as a non-responder to apomorphine 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 apomorphine (0.7 mL), although very occasionally it can be up to 10 mg apomorphine (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 Apomorphine hydrochloride Injection (10 mg/mL), the patient should be restarted on conventional antiparkinsonian therapy.

See DOSAGE AND ADMINISTRATION, Patient selection for information on patients who may be suitable for treatment by continuous SC infusion.

Continuous subcutaneous infusion of Apomine™ Solution for Infusion is administered by portable syringe driver. 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. Tolerance does not seem to occur unless the overnight period without treatment is less than 4 hours. The infusion site should be changed every 12 hours. Prolonged infusion times are associated with local adverse effects to a more severe degree.

• Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician.
• A reduction in dosage of other dopamine agonists may be considered during continuous infusion.

Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless to slightly yellow and particle free solution should be used (also see STORAGE.)

Monitoring treatment: Long term specialist supervision of patients is advised.
There is a high probability of adverse effects to Apomine™ Solution for Infusion 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**

**Symptoms**
The clinical features of overdose of Apomine™ Solution for Infusion 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.

**Treatment**
An opioid antagonist such as naloxone may be given to treat excessive vomiting, central nervous system depression and respiratory depression due to Apomine™ Solution for Infusion 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 New Zealand call 0800 764 766).

**PRESENTATION AND STORAGE CONDITIONS**
Clear glass (Type 1) vials with a bromobutyl rubber stopper and flip off cap.
100 mg/20 mL vial. Packs of 1, 5 and 10 vials.

Store below 25 °C.
Do not freeze.
Protect from light. (Keep the container in the outer carton).

After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25 °C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

**NAME AND ADDRESS OF SPONSOR**
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**POISON SCHEDULE OF THE MEDICINE**
Prescription medicine

**DATE OF PREPARATION**
03 August 2017