

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

APOMINE® Solution for Infusion, 5 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 5 mg apomorphine hydrochloride hemihydrate.

20 mL vials contain 100 mg apomorphine hydrochloride hemihydrate.

Excipients with known effect:

Sodium metabisulfite (E223) 1 mg per mL

Sodium chloride 8 mg per mL

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear and colourless to slightly yellow solution, free from visible particles.

pH of 3.3 – 4.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of 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 regimen.

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 (SC) 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 use in one patient only. From a microbiological point of view, once opened, the product may be used for a maximum of 7 days when stored below 25 °C. The infusion site should be changed every 24 hours. Discard the product no later than 7 days after first opening.

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 contraindicated 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. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk (see Section 4.4). The cardiovascular assessment should include an ECG and QT measurement. 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 (0.3 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 (0.6 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 (1.4 mL), although very occasionally it can be up to 10 mg apomorphine (2.0 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 Solution for Infusion, the patient should be restarted on conventional antiparkinsonian therapy.

See section 4.2, Patient Selection, for information on patients who may be suitable for treatment by continuous SC infusion.

Continuous SC 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 24 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.

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.

Special populations

Paediatric Population:

Apomine Solution for Infusion is contraindicated in children and adolescents up to 18 years of age. See section 4.2, Patient Selection.

Elderly:

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. See Section 4.2, Patient Selection.

4.3 Contraindications

Apomine Solution for Infusion is contraindicated in patients with a known hypersensitivity or allergy to the active substance or to any of the excipients (including sodium metabisulfite), morphine or chemically related products.

Apomine Solution for Infusion 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.

Apomine Solution for Infusion is also contraindicated in patients with inadequate renal or liver function, unstable coronary vascular disease, cerebrovascular disease, respiratory depression or CNS depression.

Apomine Solution for Infusion is contraindicated for children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

For Subcutaneous (SC) Use Only (see section 4.8)

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 section 4.3).

Apomine Solution for Infusion contains sodium metabisulfite which may cause allergic type reactions, including anaphylactic symptoms and life threatening or less severe asthmatic episodes in susceptible people (see section 4.3).

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 section 4.3).

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.

Since apomorphine may produce hypotension, even when given with domperidone pre-treatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as anti-hypertensives, and especially in patients with pre-existing 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.

When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also, medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed.

Monitoring for an effect on the QTc interval is advisable. An ECG should be performed:

- prior to treatment with domperidone
- during the treatment initiation phase
- as clinically indicated thereafter.

The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy. At each medical visit, risk factors should be revisited.

Apomorphine is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid areas of nodularity and induration (see Section 4.8).

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range (see Section 4.5).

Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients, neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients.

The use of apomorphine 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 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.

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, and/or an episode of sudden sleep onset, 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 Section 4.2, Pretreatment).

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.

Elderly population

Caution is also recommended in 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.

Paediatric population

Apomine Intermittent is contraindicated for children and adolescents under 18 years of age.

Effects on laboratory tests

Positive Coombs' tests have been reported for patients receiving apomorphine.

4.5 Interaction with other medicines and other forms of interaction

Patients selected for treatment with apomorphine are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of apomorphine therapy the patient should be monitored for unusual side-effects or signs of potentiation of effect.

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.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine.

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.

Antihypertensive and cardiac active medicinal drugs

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

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

4.6 Fertility, pregnancy and lactation

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.

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.

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 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.

4.7 Effects on ability to drive and use machines

Apomorphine has varying degrees of impairment which influences the ability to drive and use machines.

Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes 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) until such recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Very common (>10%)

Itchy nodular lesions at the injection site may be severe in patients on continuous subcutaneous infusions of Apomine. Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration (see Section 4.4), erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising, fibrosis and pain) may also occur (see Section 4.4). Care should be taken to ensure that areas of ulceration do not become infected.

Hallucinations have been reported.

Common (1-10%)

Gastrointestinal side effects including nausea and vomiting appear to be the most prevalent adverse effects, however tolerance to these effects develops rapidly. Pretreatment with domperidone may reduce or prevent these effects (see section 4.2).

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.

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

Yawning has been reported during apomorphine therapy.

Uncommon (0.1 – 1%)

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.

Apomorphine has been associated with sudden sleep onset episodes (see Section 4.4).

Postural hypotension is seen infrequently and is usually transient (See Section 4.4).

Breathing difficulties have been reported.

Local and generalised rashes have been reported. Injection site necrosis and ulceration have been reported.

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine (see Section 4.4).

Rare (0.01-0.1%)

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.

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

Other

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 Section 4.4).

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

Aggression and agitation have also been reported.

Headache has been reported.

Peripheral oedema has been reported.

Thrombus formation and pulmonary embolism have occurred with central venous infusion of apomorphine. Apomine Solution for Infusion must not be used via the intravenous route.

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 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.

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

Pharmacotherapeutic group: Dopamine agonists

ATC Code: N04B C07

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 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.

5.2 Pharmacokinetic properties

Absorption

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.

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.

Distribution and Elimination

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.

Metabolism

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 sulfate

5.3 Preclinical safety data

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.

Carcinogenicity

No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite (E223)

Sodium chloride

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See also Section 4.5.

6.3 Shelf life

Unopened: 36 months

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, once opened, the product may be used for a maximum of 7 days when stored below 25 °C.

6.4 Special precautions for storage

Store below 25 °C. Do not refrigerate or freeze.

Protect from light. (Keep the container in the outer carton).

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mg/20 mL vial: Clear glass (Type 1) vials with a bromobutyl rubber stopper and flip off cap, containing 20 mL solution for infusion. Packs of 1, 5 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 section 6.3)

Use in one patient only. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited,
PO Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

31 March 2016

10. DATE OF REVISION OF THE TEXT

09 September 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
------------------------	-----------------------------------

4.3	Contraindication clarified to include patients who a known hypersensitivity or allergy to Apomine
4.4 & 4.7	Added Precaution for patients who have experienced an episode of sudden sleep onset
4.8	Adverse Effect expanded to include the potential for severe itchy nodular lesions at the injection site.
5.1	Typographical error corrected