AUSTRALIAN PRODUCT INFORMATION – APOMINE® INTERMITTENT (Apomorphine hydrochloride hemihydrate) INJECTION CARTRIDGE

1. NAME OF THE MEDICINE

Apomorphine hydrochloride hemihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Apomine® Intermittent is a sterile solution for injection containing 10 mg/mL of apomorphine hydrochloride hemihydrate in Water for Injections BP. Each 3 mL cartridge contains 30 mg apomorphine hydrochloride hemihydrate. Sodium metabisulfite 1 mg/mL is included in the formulation as an antioxidant.

Excipient(s) with known effect:

Sodium metabisulfite

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Apomine® Intermittent is a clear, colourless to slightly yellow sterile solution for subcutaneous injection, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apomine® Intermittent 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® Intermittent 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

Dosage

The optimal dosage of Apomine® Intermittent 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.

Method of administration

Patient selection: For patients in whom conventional therapy has failed, Apomine® Intermittent 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® Intermittent to be used effectively. Adult patients through all age ranges have been successfully managed with apomorphine injections. Apomine® Intermittent is not recommended in children and adolescents below 18 years of age.

Elderly patients, in appropriate circumstances, can be successfully managed with Apomine® Intermittent.

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® Intermittent that produces an unequivocal motor response.
- Re-establish other antiparkinsonian agents.
- Determine effective treatment regimen for Apomine® Intermittent.
- 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.

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® Intermittent. When patients are stabilised with respect to dosage of Apomine® Intermittent, 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 antiparkinsonian 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).
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).

Determination of the threshold dose: Following baseline motor assessment, the patient is challenged for Apomine® Intermittent responsiveness according to the following schedule:

- 1.5 mg Apomine® Intermittent (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® Intermittent (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 Apomine® Intermittent 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 of Apomine® Intermittent (0.7 mL), although very occasionally it can be up to 10 mg of Apomine® Intermittent (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® Intermittent, 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® Intermittent according to the patient's response.

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

Apomine® Intermittent is administered by subcutaneous injection. Apomine® Intermittent injection is either into the anterior abdominal wall or anterolateral thigh. The usual dosage range is 2.4 to 3.6 mg per injection; the maximum single dose being 6 mg and the maximum total daily dose being 50 mg.

To ensure accurate dosing, either 1.0 mL insulin syringes or a D-mine® Pen should be used to administer Apomine® Intermittent injections. The injection is given in an undiluted form.

Chemical and physical in-use stability has been demonstrated for 15 days at 25°C. However, as the product contains no antimicrobial agent, for microbial reasons, once opened the contents of the cartridge should be used within 72 hours.

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.

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. For patients requiring continuous subcutaneous infusion, Apomine® Solution for Infusion should be considered.

Monitoring treatment: Long term specialist supervision of patients is advised.

There is a high probability of adverse effects to Apomine® Intermittent 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.

4.3 Contraindications

Apomine® Intermittent is contraindicated in patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically related products. Apomine® Intermittent 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.

Apomine® Intermittent is also contraindicated in patients with a known hypersensitivity to sodium metabisulfite.

4.4 Special warnings and precautions for use

For Subcutaneous Use Only (see Section 4.8 Adverse effects (undesirable effects)).

Patients sensitive to morphine or its derivatives may be sensitive to apomorphine. Apomorphine should therefore not be administered to patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically related compounds (see Section 4.3 Contraindications).

Apomine® Intermittent 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. Apomorphine is therefore contraindicated in these patients (see Section 4.3 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.

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 Section 4.2 Dose and method of administration – Pretreatment).

Use in the elderly

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

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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

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 – Pregnancy Category B3[1]

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 importance of the drug to the mother.

4.7 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 also Section 4.4 Special warnings and precautions for use).

4.8 Adverse effects (undesirable effects)

Very Common (>10%)

Itchy nodular lesions at the injection site may be severe in patients on continuous subcutaneous infusions of apomorphine, but usually disappear within 48 hours in patients receiving intermittent injections. Local bruising and fibrosis 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. 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.

Uncommon (0.1- 1%)

Increasingly severe 'on' phase dyskinesias may be associated with the use of apomorphine. They may be dose limiting and have the potential to mar the therapeutic response in some patients.

Injection site skin necrosis has been reported.

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.

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.

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 Special warnings and precautions for use).

Aggression and agitation have also been reported.

Headache has been reported.

Peripheral oedema has been reported.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

The clinical features of overdose of Apomine® Intermittent 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® Intermittent 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Apomorphine is a directly acting dopamine receptor agonist, structurally related to dopamine. Apomorphine has high *in vitro* binding affinity for the dopamine D_4 and D_5 receptor (*Ki*: 4 and 14 nM respectively), moderate affinity (*Ki*: 26 to 130 nM) for the dopamine D_2 and D_3, 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 D_1 receptor (*Ki*: 370 nM). Apomorphine exhibits no affinity for the adrenergic ß$_1$ and ß$_2$ or histamine H_1 receptors.

The effect of apomorphine as an antiparkinsonian agent is believed to be the result of direct stimulation of postsynaptic D_2 dopamine receptors, but stimulation of presynaptic D_2 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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

The peripheral pharmacokinetics of apomorphine have been studied following subcutaneous injection, subcutaneous infusion and intravenous infusion.

Absorption

Following intramuscular or subcutaneous administration, apomorphine is reported to be well absorbed. Peak plasma concentration occurs as early as three minutes following subcutaneous bolus injection. 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.

Distribution

The distribution half-life of apomorphine was found to be five minutes. The volume of distribution, plasma clearance and half-life were similar for subcutaneous injection, subcutaneous infusion and intravenous infusion.

Apomorphine reaches a concentration in the brain up to eight times higher than that in plasma, due to high lipid solubility which allows rapid equilibration between blood and tissue compartments.

Metabolism

Apomorphine is 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.

Excretion

Apomorphine is cleared rapidly. The elimination half-life ($t_{1/2}$) is about 33 minutes.

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

Water for injections

Hydrochloric acid

Sodium hydroxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See also Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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).

6.5 Nature and contents of container

Clear type I glass cartridges, with bromobutyl rubber stopper and an aluminium cap with bromobutyl rubber seal.

30 mg/3 mL cartridge. Pack of 5 cartridges.

6.6 Special precautions for disposal

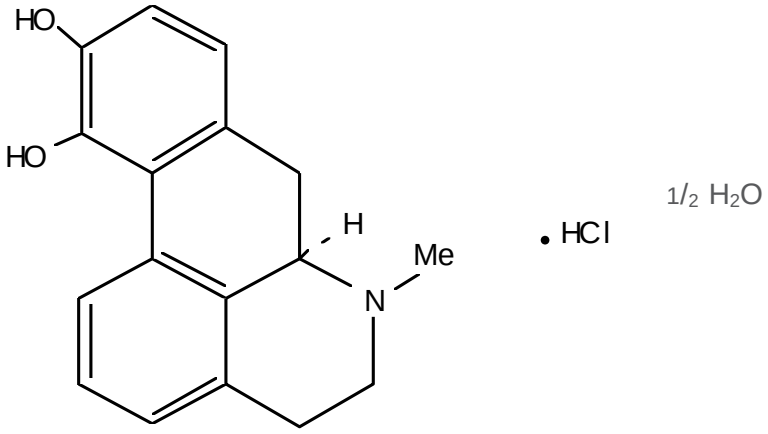
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

The pH of the injection is 2.5 to 4.0.

Chemical structure

The chemical structure is shown below:



CAS number

The CAS registry number of apomorphine hydrochloride hemihydrate is 41372-20-7.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pfizer Australia Pty Ltd
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Sydney NSW 2000
Toll Free Number: 1800 675 229

www.pfizer.com.au

9. DATE OF FIRST APPROVAL

7 June 2018

10. DATE OF REVISION

19 March 2021

Summary table of changes

Section changed	Summary of new information
4.2	In-use shelf life extended from 24 hours to 72 hours.