

APOMORPHINE 10 MG/ML SOLUTION FOR INJECTION

PL 12406/0024

UKPAR

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APOMORPHINE 10 MG/ML SOLUTION FOR INJECTION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Archimedes Pharma UK Limited a Marketing Authorisation (licence) for the medicinal product Apomorphine 10 mg/ml solution for injection (product licence number 12406/0024) on 26 September 2007. This medicine is available by prescription for the treatment of the symptoms of Parkinson's disease. It helps to reduce the amount of time a Parkinson's sufferer will spend in an 'off' or immobile state.

Apomorphine 10 mg/ml solution for injection contains the active ingredient apomorphine, which belongs to a group of medicines called dopamine agonists. Dopamine is a naturally occurring chemical in the brain that controls movement and balance and is essential to the proper functioning of the central nervous system. In Parkinson's disease, not enough dopamine is produced by the brain. Dopamine agonists can mimic the effects of dopamine in the brain and can provide relief from the symptoms of Parkinson's disease.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Apomorphine 10 mg/ml solution for injection outweigh the risks, hence a Marketing Authorisation has been granted.

APOMORPHINE 10 MG/ML SOLUTION FOR INJECTION

PL 12406/0024

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Apomorphine 10 mg/ml solution for injection (PL 12406/0024) on 26 September 2007. The product is a prescription-only medicine (POM).

This abridged application was submitted according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to Britaject Injection 10 mg/ml (PL 04483/0038; Britannia Pharmaceuticals Ltd) first authorised on 10 August 1993.

Apomorphine 10 mg/ml solution for injection contains 10 mg/ml of the active ingredient apomorphine (presented as apomorphine hydrochloride), a dopamine agonist. It is indicated for the treatment of disabling motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease, which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. The product is for subcutaneous use by intermittent bolus injection or by continuous subcutaneous infusion. Apomorphine should not be used via the intravenous route. The dosage form is in two sizes (2 ml and 5 ml) of glass ampoule.

PHARMACEUTICAL ASSESSMENT

ACTIVE INGREDIENT

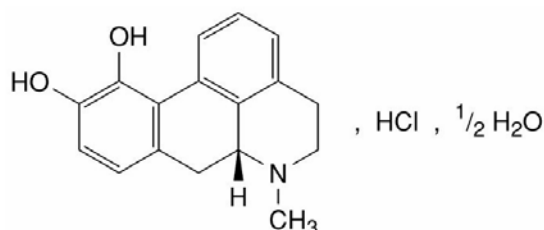
Apomorphine Hydrochloride

USAN/BAN: Apomorphine hydrochloride

Compendial name
(Ph.Eur/BP/USP): Apomorphine hydrochloride

Chemical Name: (6*R*)-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate.

Structure:



Molecular Formula: C₁₇H₁₇NO₂·HCl, $\frac{1}{2}$ H₂O

Molecular Weight: 312.8

General properties: White or greyish-white crystals or microcrystalline powder, melts with decomposition between 225-235°C. It is soluble in water and ethanol (96%), slightly soluble in ether and practically insoluble in chloroform. Apomorphine hydrochloride molecule contains one chiral centre and its absolute configuration is R.

Specific optical rotation: -48 to -52.0° (Ph.Eur. method).

The specification for apomorphine hydrochloride complies with the monograph requirements of Ph Eur/USP and includes appropriate additional controls.

Analytical procedures are either pharmacopoeial or in-house methods that have been suitably validated; all analytical procedures are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses are supplied for typical batches of apomorphine hydrochloride and the data show consistent compliance with the proposed specification.

A reference standard is not required for testing but a suitable Ph.Eur identification test is used.

The active ingredient is packaged in an appropriate container closure system that ensures its stability.

A retest period of 3 years is proposed for the apomorphine hydrochloride when stored at or below 25°C in the absence of light. This retest period is supported by the data submitted.

DRUG PRODUCT

Composition

Apomorphine 10 mg/ml solution for injection is a sterile aqueous solution presented in either 2 ml or 5 ml clear Type 1 neutral glass ampoules. It has the following qualitative composition:

Ingredient	Function	Quality Standard
Apomorphine HCl	Active	Ph.Eur
Sodium metabisulphite	Anti-oxidant	Ph.Eur
Sodium hydroxide	pH adjustment	Ph.Eur
Hydrochloric acid	pH adjustment	Ph.Eur
Water for Injections	solvent	Ph.Eur

All ingredients comply with their respective current Ph.Eur. requirements. Satisfactory certificates of analysis have been provided for all excipients. No materials of human or animal origin are used in the manufacture of these excipient materials.

There were no novel excipients used and no overages.

Essential similarity

Evidence of essential similarity between the applicant's product and the the reference product, in relation to physical and chemical parameters (including impurity profiles), has been provided. No bioequivalence studies have been submitted, or are required, for the product as it is same type of solution and has the same concentration of active and the same excipients as the reference product.

Manufacture

A satisfactory manufacturing formula for a typical production batch is provided. Manufacture of the bulk solution takes place in conditions that are in line with GMP requirements for aseptic preparation. In-process controls are appropriate considering the

nature of the product and the method of manufacture. Process validation has been carried out on batches of each fill size. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch analytical data are provided for batches of each ampoule size. These batches all comply with the release specification. Assays of the reference materials used are provided and are satisfactory.

Container Closure System

Ph.Eur, Type I, neutral glass ampoules. Certificate of Analysis and batch testing results from the supplier are provided.

Finished Product Stability

Stability storage conditions and the testing schedule are given, and are in line with guideline requirements. The data provided so far shows no significant changes in any of the parameters monitored.

Based on the results, a shelf life of 24 months is proposed when stored below 25°C and ampoules are kept in the outer carton.

Conclusion

Grant of a Marketing Authorisation is pharmaceutically satisfactory.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

INDICATIONS

The proposed indication for this product is:

“The treatment of disabling motor fluctuations (“on-off” phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.”

Medical Assessor’s Comment: The indications are appropriate for a product of this type.

DOSE AND DOSE SCHEDULE

The proposed dosage regimen is:

“Apomorphine 10mg/ml solution for injection is for subcutaneous use by intermittent bolus injection. Apomorphine 10mg/ml solution for injection may also be administered as a continuous subcutaneous infusion. Apomorphine 10mg/ml solution for injection may be diluted with sodium chloride solution 0.9% or Water for Injections.

Apomorphine must not be used via the intravenous route.

Dosage

Adults

Administration

Selection of patients suitable for apomorphine 10mg/ml solution for injection

Patients selected for treatment with Apomorphine 10mg/ml solution for injection should be able to recognise the onset of their ‘off’ symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

It is essential that the patient is established on domperidone, usually 20mg three times daily for at least two days prior to initiation of therapy.

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson’s disease (e.g. neurologist). The patient’s treatment with levodopa, with or without dopamine agonists, should be optimised before starting Apomorphine 10mg/ml solution for injection treatment.

Determination of the threshold dose

The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:

1mg of apomorphine HCl (0.1ml), that is approximately 15 to 20 micrograms/kg, may be injected subcutaneously during a hypokinetic or ‘off’ period and the patient observed over 30 minutes for a motor response.

If no response, or an inadequate response, is obtained a second dose of 2mg apomorphine HCl (0.2ml) is injected subcutaneously and the patient observed for a for an adequate response for a further 30 minutes.

The dosage may be increased by incremental injections with at least a 40 minute interval between succeeding injections, until a satisfactory motor response is obtained.

Establishment of treatment

Once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response.

The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, remains relatively constant for each patient.

Precautions on continuing treatment

The daily dose of apomorphine 10mg/ml solution for injection varies widely between patients, typically within the range of 3mg to 30mg, given as 1 to 10 injections and sometimes as many as 12 separate injections per day.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100mg and that individual bolus injections should not exceed 10mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa, this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Continuous Infusion

Patients who have shown a good 'on' period response during the initiation stage, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per day), may be commenced on or transferred to continuous subcutaneous infusion as follows:

Continuous infusion is started at a rate of 1mg apomorphine HCl (0.1ml) per hour then increased according to the individual response. Increases in the infusion rate should not exceed 0.5mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1mg and 4mg (0.1ml and 0.4ml), equivalent to 0.015 – 0.06mg/kg/hour. Infusions should run for waking hours only. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours.

Patients may need to supplement their continuous infusion with intermittent bolus boosts via the pump system as necessary, and as directed by their physician.

A reduction in dosage of other dopamine agonists may be considered during continuous infusion.

Children and adolescents

Apomorphine 10mg/ml solution for injection is contraindicated for children and adolescents up to 18 years of age (see section 4.3 Contraindications).

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 apomorphine has not differed from that of younger patients.

Renal Impairment

A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment (see Section 4.4 – Special warnings and precautions for use)."

Medical Assessor's Comments: This dosage regimen is suitable for a product of this type.

TOXICOLOGY

A pharmaco-toxicological expert report is included. The author has appropriate qualifications and experience.

CLINICAL PHARMACOLOGY

No new pharmacological data have been submitted. There is no need for determining the bioavailability or showing bioequivalence, the subcutaneous route providing 100% bioavailability.

The clinical pharmacology has been suitably summarised in the clinical expert report.

EFFICACY

No new clinical data have been submitted with this application. None are required, but a bibliographic review supporting both the efficacy and safety of apomorphine is provided in the clinical expert report.

SAFETY

The adverse effects of apomorphine are predictable in light of the pharmacological actions of the drug. Nausea and vomiting, the most frequent, may be controlled by domperidone.

EXPERT REPORT

A clinical expert report has been submitted by a consultant in pharmaceutical medicine.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The Summary of Product Characteristics for this product is satisfactory.

PATIENT INFORMATION LEAFLET

The patient information leaflet for this product is satisfactory.

LABELLING

Satisfactory

DISCUSSION

This Marketing Authorisation Application is satisfactory.

RECOMMENDATION

A marketing authorisation may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Apomorphine 10 mg/ml solution for injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

The efficacy of apomorphine has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and some benefit has been shown to be associated with Apomorphine 10 mg/ml solution for injection. The risk benefit is therefore considered to be positive.

APOMORPHINE 10 MG/ML SOLUTION FOR INJECTION

PL 12406/0024

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 18 August 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12 August 2005
3	Following assessment of the application the MHRA requested further information on the quality dossier on 22 January 2004 and on the clinical dossier on 23 April 2004. The applicant responded to the MHRA's requests, providing further information on 29 October 2004
4	The MHRA requested further information on the quality dossier on 26 August 2005. The applicant responded to the MHRA's requests, providing further information on 24 November 2005
5	The MHRA requested further information on the quality dossier on 26 April 2006. The applicant responded to the MHRA's requests, providing further information on 9 May 2006
6	The MHRA requested further information on the quality dossier on 25 July 2006. The applicant responded to the MHRA's requests, providing further information on 25 July 2006
7	The MHRA requested further information on the clinical dossier on 23 July 2007. The applicant responded to the MHRA's requests, providing further information on 24 July 2007
8	The application was determined on 26 September 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Apomorphine 10mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10mg apomorphine hydrochloride

2ml contains 20mg apomorphine hydrochloride

5ml contains 50mg apomorphine hydrochloride

For excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection

A clear, colourless to pale yellow solution. .

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of disabling motor fluctuations (“on-off” phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.

4.2 Posology and method of administration

Apomorphine 10mg/ml solution for injection is for subcutaneous use by intermittent bolus injection. Apomorphine 10mg/ml solution for injection may also be administered as a continuous subcutaneous infusion. Apomorphine 10mg/ml solution for injection may be diluted with sodium chloride solution 0.9% or Water for Injections.

Apomorphine must not be used via the intravenous route.

Dosage

Adults

Administration

Selection of patients suitable for apomorphine 10mg/ml solution for injection

Patients selected for treatment with Apomorphine 10mg/ml solution for injection should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

It is essential that the patient is established on domperidone, usually 20mg three times daily for at least two days prior to initiation of therapy.

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting Apomorphine 10mg/ml solution for injection treatment.

Determination of the threshold dose

The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:

1mg of apomorphine HCl (0.1ml), that is approximately 15 to 20 micrograms/kg, may be injected subcutaneously during a hypokinetic or 'off' period and the patient observed over 30 minutes for a motor response.

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The dosage may be increased by incremental injections with at least a 40 minute interval between succeeding injections, until a satisfactory motor response is obtained.

Establishment of treatment

Once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response.

The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, remains relatively constant for each patient.

Precautions on continuing treatment

The daily dose of apomorphine 10mg/ml solution for injection varies widely between patients, typically within the range of 3mg to 30mg, given as 1 to 10 injections and sometimes as many as 12 separate injections per day.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100mg and that individual bolus injections should not exceed 10mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa, this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Continuous Infusion

Patients who have shown a good 'on' period response during the initiation stage, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per day), may be commenced on or transferred to continuous subcutaneous infusion as follows:

Continuous infusion is started at a rate of 1mg apomorphine HCl (0.1ml) per hour then increased according to the individual response. Increases in the infusion rate should not exceed 0.5mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1mg and 4mg (0.1ml and 0.4ml), equivalent to 0.015 – 0.06mg/kg/hour. Infusions should run for waking hours only. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours.

Patients may need to supplement their continuous infusion with intermittent bolus boosts via the pump system as necessary, and as directed by their physician.

A reduction in dosage of other dopamine agonists may be considered during continuous infusion.

Children and adolescents

Apomorphine 10mg/ml solution for injection is contraindicated for children and adolescents up to 18 years of age (see section 4.3 Contraindications).

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 apomorphine has not differed from that of younger patients.

Renal Impairment

A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment (see Section 4.4 – Special warnings and precautions for use).

4.3 Contraindications

In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

Intermittent apomorphine treatment is not suitable for patients who have an ‘on’ response to levodopa that is marred by severe dyskinesia or dystonia.

Apomorphine 10mg/ml solution for injection should not be administered to patients who have a known sensitivity to apomorphine or any of the other ingredients of the product.

Apomorphine is contra-indicated in children and adolescents-under 18 years of age.

4.4 Special warnings and precautions for use

Apomorphine should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

Extra caution is recommended during initiation of therapy in elderly and/or debilitated 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 antihypertensives, and especially in patients with pre-existing postural hypotension.

Apomorphine 10mg/ml solution for injection contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm. It also contains sodium at less than 1mmol (23mg) per ml.

Haemolytic anaemia has been reported in patients treated with levodopa and apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa when given concomitantly with apomorphine.

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range (see Section 4.5 – Interaction with other medicinal products and other forms of interaction).

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.

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.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including apomorphine.

4.5 Interaction with other medicinal products and other forms of interactions

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.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications.

If neuroleptic medicinal products have to be used in patients with Parkinson's disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and/or syringe-driver (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy).

4.6 Pregnancy and lactation

Pregnancy

Due to the age of the treated population, the occurrence of pregnancy is improbable. Animal studies are insufficient with respect to the effects on pregnancy, embryo-fetal development, parturition and postnatal development (See section 5.3). The potential risk for humans is unknown.

Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age.

Lactation

It is not known whether apomorphine is excreted in breast milk. However, breast-feeding should be avoided during apomorphine therapy.

4.7 Effects on 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 (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see Section 4.4 – Special warnings and precautions for use).

4.8 Undesirable 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 these may persist and give rise to areas of erythema, tenderness and induration. Panniculitis has been reported from those 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 the use of ultrasound (if available) to areas of nodularity and induration.

Common (1% to 10%)

Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone (see Section 4.2 – Posology and method of administration).

Transient sedation with each dose of apomorphine at the start of therapy may occur; this usually resolves over the first few weeks.

Apomorphine is associated with somnolence.

Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy.

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 therapy.

Uncommon (0.1% to 1%)

Postural hypotension is seen infrequently and is usually transient (see Section 4.4 – Special warnings and precautions for use).

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.

Local and generalised rashes have been reported.

Haemolytic anaemia has been reported in patients treated with levodopa and apomorphine.

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

Breathing difficulties have been reported.

Rare (0.01% to 0.1%)

Eosinophilia has rarely occurred during treatment with apomorphine .

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

Unknown:

Patients treated with dopamine agonists for treatment of Parkinson's disease, including apomorphine, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

4.9 Overdose

There is little clinical experience of overdosage with apomorphine by this route of administration. Symptoms of overdosage may be treated empirically as suggested below:

Excessive emesis may be treated with domperidone

Respiratory depression may be treated with naloxone.

Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed.

Bradycardia may be treated with atropine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists

ATC Classification: N04B C07

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa.

Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release), its actions on Parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans.

5.2 Pharmacokinetic properties

Apomorphine, a potent agonist, has been used in acute and chronic studies of Parkinsonism and other neurological disorders. After subcutaneous injection its fate can be described by a two-compartment model, with a distribution half-life of 5 (± 1.1) minutes and an elimination half-life of 33 (± 3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid. From the drug absorption, volume of injection, S.C. infusion, and I.V. infusion, it can be concluded that apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4 to 12 minutes), and that the brief duration of a clinical action of the drug (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine in humans does not show enantiomer interconversion nor methylation into (iso)apocodeine. Approximately ten per cent of the metabolism is by glucuronidation and sulphonation.

5.3 Preclinical safety data

Repeat dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the Summary of Product Characteristics.

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in the *in vivo* studies performed.

There are no data on fertility and embryo-foetal toxicity. No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite

Hydrochloric acid

Sodium hydroxide

Water for Injections

6.2 Incompatibilities

As with all parenteral solutions, incompatibility of additive medications with the solution must be assessed before addition. In the absence of compatibility studies, this solution must not be mixed with other medicinal products, except sodium chloride 0.9% and Water for Injections.

6.3 Shelf life

Unopened: 2 years

Shelf life after first opening the ampoule: Immediate use

Shelf life after dilution: 24 hours

6.4 Special precautions for storage

Do not store above 25°C. Keep ampoules in the outer carton.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when the product is diluted with sodium chloride 0.9% injection or Water for Injections. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Clear, colourless type I glass ampoules containing 2ml solution for injection, supplied in packs of 5 or 10 ampoules.

Clear, colourless type I glass ampoules containing 5ml solution for injection, supplied in packs of 5 or 10 ampoules.

6.6 Special precautions for disposal

Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless to pale yellow solutions should be used.

For single use only. Any unused solution should be discarded.

Apomorphine 10mg/ml solution for injection is compatible with sodium chloride solution 0.9% and Water for Injections.

7 MARKETING AUTHORISATION HOLDER

Archimedes Pharma UK Limited
250 South Oak Way
Green Park
Reading
Berkshire
RG2 6UG
UK

8 MARKETING AUTHORISATION NUMBER

PL12406/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/09/2007

10 DATE OF REVISION OF THE TEXT

26/09/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

APOMORPHINE 10mg/ml SOLUTION FOR INJECTION

Please read this leaflet carefully BEFORE you start using apomorphine 10mg/ml solution for injection.

- Keep this leaflet. You may need to read it again.
- This leaflet does not tell you everything about your medicine. If you have any questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Each ml contains 10mg apomorphine hydrochloride as active ingredient.

The injection also contains the following inactive ingredients:

Sodium metabisulphite and Water for Injections.

The pH (acidity) of the injection solution is occasionally adjusted by adding a small quantity of hydrochloric acid or sodium hydroxide.

Apomorphine 10mg/ml solution for injection is available in 2ml and 5ml ampoules. The ampoules are available in pack sizes of 5 or 10 ampoules.

The Marketing Authorisation is held by: Archimedes Pharma UK Ltd., 250 South Oak Way, Green Park, Reading, Berkshire RG2 6UG, UK.

Apomorphine 10mg/ml solution for injection is manufactured by Celltech Manufacturing Services Limited, Vale of Bardsley, Ashton-under-Lyne, Lancashire, OL7 9RR, UK.

1. WHAT APOMORPHINE 10mg/ml SOLUTION FOR INJECTION IS USED FOR

Apomorphine is one of several medicines, known as dopamine agonists, used to treat Parkinson's disease. It helps to reduce the amount of time spent in an "off" or immobile state. Your doctor or nurse will help you to recognise the signs of when to use your medicine.

If you need any further information on Parkinson's disease, please ask your doctor or pharmacist.

2. BEFORE YOU USE APOMORPHINE 10mg/ml SOLUTION FOR INJECTION

Do not use apomorphine 10mg/ml solution for injection if you:

- think you may be pregnant or are trying to become pregnant.
- are breast feeding.
- have breathing difficulties.
- have dementia or Alzheimer's disease.

- have liver problems.
- are allergic to morphine, morphine derivatives, sulphites, metabisulphites or any of the ingredients of apomorphine hydrochloride injection.
- have severe dyskinesia (involuntary movements).
- have any disorder, other than Parkinson's disease, which affects the brain or spinal cord.
- are under 18 years of age.

Take special care with apomorphine 10mg/ml solution for injection if you:

- have heart disease or poor circulation.
- have kidney problems.
- have low blood pressure (feel faint or dizzy upon standing).
- suffer from nausea and vomiting.
- have neuropsychiatric problems (confusion, hallucinations).

Pregnancy and breast-feeding

Apomorphine 10mg/ml solution for injection should not be used if you are pregnant or breast-feeding.

Driving and using machines

- Apomorphine 10mg/ml solution for injection may make you feel sleepy.
- If you experience excessive drowsiness, do not drive because apomorphine 10mg/ml solution for injection could stop you driving safely.
- If you experience excessive drowsiness, do not operate any tools or machines as this may put you or others at serious risk of injury.

Important information about some of the ingredients of apomorphine 10mg/ml solution for injection

Apomorphine 10mg/ml solution for injection contains sodium metabisulphite which may rarely cause severe allergic reactions and breathing difficulties.

Contains sodium. Apomorphine 10mg/ml solution for injection contains less than 1mmol sodium (23mg) per ml and is essentially 'sodium-free'.

Taking/using other medicines

Tell your doctor if you are taking any of the following medicines:

- neuroleptic medicines such as clozapine.
- medicines for the treatment of high or low blood pressure.

Please note that these statements may also apply to products used some time ago or at some time in the future.

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine – even those not prescribed but bought over the counter.

3. HOW TO USE APOMORPHINE 10mg/ml SOLUTION FOR INJECTION

Your doctor or pharmacist will have

told you how much of your medicine you should inject and how often. This will have been determined by your personal needs during your initiation treatment in hospital or at a clinic. The dose is typically in the range of 3mg to 30mg per day, injected under the skin (subcutaneously) 1 to 10 times a day at the first sign of an unpredictable "off" period. If you are not sure how much to use, ask your doctor or pharmacist.

Apomorphine 10mg/ml solution for injection is usually injected under the skin of the upper arms, thighs or abdomen. However, you should inject apomorphine 10mg/ml solution for injection where your doctor or nurse has told you to.

You should not exceed a total daily dose of 100mg and you should not inject more than 10mg at any one time, unless your doctor has told you to.

Some patients have a continuous infusion of apomorphine 10mg/ml solution for injection. Your doctor or nurse will decide if you need this form of treatment and which dose is best for you. The usual dose is between 1mg and 4mg per hour, usually during waking hours.

If you use more apomorphine 10mg/ml solution for injection than you should

It is important not to inject more than the prescribed dose. If you, or someone near to you, has used more apomorphine 10mg/ml solution for injection than was prescribed, contact your doctor or go to the nearest hospital emergency department immediately. Remember to take any remaining apomorphine 10mg/ml solution for injection and the injection container or this leaflet with you so the doctors know what has been used.

4. POSSIBLE SIDE-EFFECTS

Like all medicines, apomorphine 10mg/ml solution for injection can have side-effects.

Tell your doctor or pharmacist if you think your medicine is making you feel unwell or if you experience any of the following:

- feeling light-headed or restless
- feeling sick or being sick*
- confusion or hallucinations
- feeling drowsy
- low blood pressure (feeling faint or dizzy upon standing)
- lumps under the skin at the site of injection which are sore and troublesome
- increased involuntary movements or worsening tremors during "on" periods
- rashes
- breathing difficulties
- pathological gambling (failure to resist the impulse to gamble despite serious personal or family consequences)
- increased sex drive
- hypersexuality (altered sexual interest

and behaviour causing concern to the patient or others)

- anaemia or low blood cell count**

* Most patients take domperidone to stop them feeling or being sick. If you are taking domperidone and still have sickness, or if you are not taking domperidone and have sickness, tell your doctor or nurse as soon as possible.

** Anaemia (or blood disorders) is an uncommon side-effect which can occur in patients taking levodopa (another medicine for the treatment of Parkinson's disease). If you are taking levodopa as well as apomorphine 10mg/ml solution for injection, your doctor should arrange for you to have blood tests at regular intervals.

If you notice any side-effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING APOMORPHINE 10mg/ml SOLUTION FOR INJECTION

The ampoules should be stored in the outer carton to protect from light. Keep it in a safe place, out of the reach and sight of children.

Do not store apomorphine 10mg/ml solution for injection above 25°C.

Withdraw the required contents from the ampoule immediately after opening and discard any unused contents.

Used syringes, needles and ampoules should be discarded in a "sharps" bin or other suitable container. When your "sharps" bin or container is full, please give it to your district nurse, pharmacist or doctor for safe disposal.

Do not use apomorphine 10mg/ml solution for injection if the solution has turned green. Use it only if the solution is clear and colourless or pale yellow.

Do not keep the medicine if your doctor decides to stop treatment. Return it to your pharmacist who will arrange for its safe disposal.

Use by date

Do not use apomorphine 10mg/ml solution for injection after the expiry date. This is shown on the injection label and the carton.

It starts with the letters 'Exp' followed by the month and year. The injection should not be used after the end of that month. If you are not sure when this is, check with your doctor or pharmacist.

The information in this leaflet only applies to apomorphine 10mg/ml solution for injection.

This leaflet was revised in September 2007.

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LABELLING

2 ml ampoule label:

2ml
Apomorphine
10mg/ml
solution for injection
Each 2ml ampoule contains
20mg apomorphine
hydrochloride
For subcutaneous injection
or infusion

EXP:
BN:

5 ml ampoule label:

5ml
Apomorphine
10mg/ml
solution for injection
Each 5ml ampoule contains
50mg apomorphine
hydrochloride
For subcutaneous injection
or infusion

EXP:
BN:

