

**APOMORPHINE HYDROCHLORIDE 10MG/ML SOLUTION  
FOR INJECTION**

**PL 17507/0051**

**UKPAR**

**TABLE OF CONTENTS**

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 11
Summary of Product Characteristics	Page 12
Patient Information Leaflet	Page 19
Labelling	Page 21

**APOMORPHINE HYDROCHLORIDE 10MG/ML SOLUTION  
FOR INJECTION**

**PL 17507/0051**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Auden McKenzie Limited a Marketing Authorisation (licence) for the medicinal product Apomorphine Hydrochloride 10mg/ml Solution for Injection (PL 17507/0051) on 9<sup>th</sup> July 2007. This is a prescription-only medicine (POM) for the treatment of the symptoms of Parkinson's disease. It helps to reduce the amount of time spent in an 'off' or immobile state.

Apomorphine Hydrochloride 10mg/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 of 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 Hydrochloride 10 mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.

**APOMORPHINE HYDROCHLORIDE 10MG/ML SOLUTION  
FOR INJECTION**

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**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment (including statistical assessment)	Page 9
Overall conclusions and risk benefit assessment	Page 10

## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Apomorphine Hydrochloride 10mg/ml Solution for Injection (PL 17507/0051) on 9<sup>th</sup> July 2007. The product is a prescription-only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Britaject (PL 04483/0038 Britannia Pharmaceuticals Ltd) first authorised in 1993.

The product contains the active ingredient apomorphine (presented as apomorphine hydrochloride), a dopamine agonist, and 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. No paediatric development plan exists for this product, which is permissible in view of the indication.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### Apomorphine hydrochloride

Nomenclature:

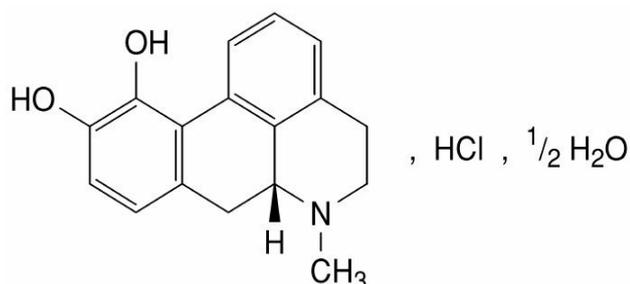
rINNM / BAN: Apomorphine Hydrochloride

USAN: Apomorphine Hydrochloride

Chemical names:

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

Structure:



C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>.HCl, $\frac{1}{2}$ H<sub>2</sub>O

MW: 312.8

CAS No.: 41372-20-7

Physical form: White or greyish-white crystals or microcrystalline powder

Solubility: Soluble in water and ethanol (96%), slightly soluble in ether and practically insoluble in chloroform

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Apomorphine hydrochloride is packed in heat-sealed polythene bags contained in tins. The tins are sealed with polythene tape and tamper-proof seals. This packaging is satisfactory. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data has been provided by the finished product manufacturer and it complies with the specifications.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

Appropriate stability data have been generated supporting a retest period of 3 years, when stored at 25°C or below in the absence of light.

**DRUG PRODUCT****Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely sodium metabisulphite, sodium hydroxide, hydrochloric acid, and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

There are no materials of animal or human origin contained in or used in the manufacturing process for the proposed products.

There were no novel excipients used and no overages.

A satisfactory summary of the development of the product leading to adoption of the manufacturing process has been provided.

**Dissolution and impurity profiles**

Impurity profiles for the drug product were found to be similar to those for the reference products, and all the impurities are within the specification limits.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

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 strength. 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 data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The drug product is packaged in type I clear glass ampoules of Ph. Eur. Specifications, with volumes of 2ml or 5ml. The applicant tests ampoules from different packs for appearance and dimensions. Specifications and Certificates of Analysis for both packaging types used (2ml and 5ml) have been provided. The ampoules are packed into cartons in packs of five with a patient information leaflet.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. No specific storage conditions have been set.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form.

## **PRECLINICAL ASSESSMENT**

This application for a generic product claims essential similarity to Britaject. (PL 04483/0038 Britannia Pharmaceuticals Ltd), which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

## **CLINICAL ASSESSMENT**

### **CLINICAL PHARMACOLOGY**

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

### **EFFICACY**

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

### **SAFETY**

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

The safety profile of apomorphine has been well established in more than 10 years of clinical use.

The reference product is established and the application is based upon essential similarity with the reference product.

### **EXPERT REPORT**

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

### **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The proposed SPC has been updated and brought into line with that for the reference product and is satisfactory.

### **PATIENT INFORMATION LEAFLET (PIL)**

The PIL has been amended with regard to the revised SPC and is satisfactory.

### **LABELLING**

The labelling is satisfactory.

### **CONCLUSIONS**

The grounds for establishing essential similarity with the reference product are considered adequate. The product literature is approved.

The grant of a marketing authorisation is recommended.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Apomorphine Hydrochloride 10mg/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 applications of this type.

### **EFFICACY**

The applicant's Apomorphine Hydrochloride 10 mg/ml Solution for Injection is considered to be essentially similar to the reference product Britaject (PL 04483/0038 Britannia Pharmaceuticals Ltd).

Recent safety updates have been included in the product literature..

The approved SPC, PIL and labelling are satisfactory and consistent with that for Britaject.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with apomorphine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**A POMORPHINE HYDROCHLORIDE 10MG/ML SOLUTION  
FOR INJECTION****PL 17507/0051****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 13 <sup>th</sup> February 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 20 <sup>th</sup> February 2006
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 15 <sup>th</sup> February 2007, and further information relating to the quality dossiers on 19 <sup>th</sup> May 2006 and 2 <sup>nd</sup> January 2007.
4	The applicant responded to the MHRA's requests, providing further information on 20 <sup>th</sup> June 2007 for the clinical sections, and again on 18 <sup>th</sup> September 2006 and 21 <sup>st</sup> March 2007 for the quality sections.
5	The applications were determined on 9 <sup>th</sup> July 2007

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Apomorphine Hydrochloride 10 mg/ml solution for injection is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Apomorphine Hydrochloride 10 mg/ml Solution for Injection

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2 ml contains 20 mg apomorphine hydrochloride 0.5 H<sub>2</sub>O

5 ml contains 50 mg apomorphine hydrochloride 0.5 H<sub>2</sub>O

For a full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Solution for injection.

Solution is clear and colourless.

### 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 10 mg/ml Solution for Injection is for subcutaneous use by intermittent bolus injection.

Apomorphine 10 mg/ml Solution for Injection may also be administered as a continuous subcutaneous infusion by minipump and or syringe-driver (see section 6.6, instructions for use and handling).

Apomorphine must not be used via the intravenous route.

#### Adults

Patients selected for treatment with apomorphine 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 20 mg 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 treatment.

#### Determination of the threshold dose.

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

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

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

The dosage may be increased by incremental injections with at least a forty 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 varies widely between patients, typically within the range of 3-30 mg, given as 1-10 injections and sometimes as many as 12 separate injections per day.

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

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 by minipump and or syringe-driver (see section 6.6, instructions for use and handling) as follows:-

Continuous infusion is started at a rate of 1 mg apomorphine hydrochloride (0.1 ml) per hour then increased according to the individual response. Increases in the infusion rate should not exceed 0.5 mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.1 ml and 0.4 ml), equivalent to 0.015 - 0.06 mg/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 10 mg/ml Solution for Injection is contraindicated for children and adolescents under 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 warning and precautions for use).

Hepatic impairment:

Apomorphine 10 mg/ml Solution for Injection is contraindicated in patients with hepatic insufficiency (see section 4.3, contraindications).

**4.3 CONTRAINDICATIONS**

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

Intermittent apomorphine hydrochloride treatment is not suitable for patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia,.

Apomorphine should not be administered to patients who have a known hypersensitivity to opioids, apomorphine or any excipients of the medicinal product.

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

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Apomorphine hydrochloride 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 10 mg/ml Solution for Injection contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

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. This product contains less than 1 mMol sodium (<23 mg) per 5 ml solution and is essentially 'sodium free'.

**4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS 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.

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).

The possible effects of apomorphine on the plasma concentrations of other medicinal products may not have 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 Products

Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products. See section 4.4 special warnings and precautions for use above.

### **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 HCl 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 also 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 HCl these may persist and give rise to areas of erythema, tenderness and induration. Panniculitis has been reported from these patients where a skin biopsy has been undertaken. Care should be taken to ensure that areas of ulceration do not become infected. Pruritus may occur at the site of injection.

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

#### **Common (1-10%):**

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

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

Apomorphine is associated with somnolence.

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

**Uncommon (0.1-1%):**

Postural hypotension is seen infrequently and is usually transient (See 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%-0.1%):**

Eosinophilia has rarely occurred during treatment with apomorphine HCl.

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

**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 SYMPTOMS, EMERGENCY PROCEDURES, ANTIDOTES**

There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose 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**

After subcutaneous injection of apomorphine its fate can be described by a two-compartment model, with a distribution half-life of 5 ( $\pm$ 1.1) minutes and an elimination half-life of 33 ( $\pm$ 3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the active substance distribution being best described by a two-compartment model. 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. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described.

**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 SmPC.

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 (E223)

Water for Injections

0.1N Hydrochloric acid\*

0.1N Sodium hydroxide\*

\*for pH adjustment only

**6.2 INCOMPATIBILITIES**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**6.3 SHELF LIFE**

24 months.

*Subcutaneous infusion:* From a microbiological point of view, the product should be used immediately when prepared for subcutaneous infusion. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours when stored between 2-8°C.

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Keep the ampoules in the outer carton.

This medicinal product does not require any special storage conditions.

For storage of product (when prepared as a subcutaneous infusion) see section 6.3.

**6.5 NATURE AND CONTENTS OF CONTAINER**

Type I glass ampoules containing 2ml solution for injection, in packs of 5 ampoules.

Type I glass ampoules containing 5ml solution for injection, in packs of 5 ampoules.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND ANY OTHER HANDLING**

Do not use if the solution has turned green.

The solution should be inspected visually prior to use. Only clear and colourless solutions should be used.

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

Continuous infusion and the use of a minipump and or syringe-driver.

The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient.

- 7      MARKETING AUTHORISATION HOLDER**  
Auden McKenzie Ltd  
Unit 30 Stadium Business Centre  
North End Road  
Wembley  
Middlesex  
HA9 0AT
- 8      MARKETING AUTHORISATION NUMBER(S)**  
PL 17507/0051
- 9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE    AUTHORISATION**  
09/07/2007
- 10     DATE OF REVISION OF THE TEXT**  
09/07/2007

## PATIENT INFORMATION LEAFLET

Rare (affecting 1-10 patients out of 10,000)

- Severe allergic reactions and asthma caused by sodium metabisulphite can occur rarely. Tell your doctor if you suddenly have difficulty in breathing, or if you think you have an allergic reaction.

### Unknown

- Some patients may experience failure to resist gambling impulses despite serious personal or family consequences. Some patients may suffer from increased sexual drive and a desire for sexual behaviour which is of significant concern to the individual or to others. If you experience any of these symptoms, you must tell your doctor immediately.

Tell your doctor or nurse if you have any of these side effects or if you notice any other unwanted effects.

### 6. Storing Apomorphine Hydrochloride 10mg/ml Solution for Injection

Keep your Apomorphine Hydrochloride 10mg/ml Solution for Injection in a safe place where children cannot see or reach them. It can be dangerous to children. This medicinal product does not require any special storage conditions. Do not put the ampoules into another container. Do not use Apomorphine Hydrochloride 10mg/ml Solution for Injection after the expiry date printed on the carton and labels.

### 7. What is in Apomorphine Hydrochloride 10mg/ml Solution for Injection?

The name of your medicine is Apomorphine Hydrochloride 10mg/ml Solution for Injection and its active ingredient is apomorphine hydrochloride. There are 10 milligrams of apomorphine in each ml. The ampoules contain either 2 ml or 5 ml of solution and are available in packs of 5 ampoules. Other ingredients in the solution are sodium metabisulphite (E223), water, hydrochloric acid and sodium hydroxide (inactive ingredients). This medicinal product contains less than 1 mMol sodium (less than 23 mg) per 2 ml and 5 ml ampoule, i.e. it is essentially 'sodium free'.

Only marketed pack sizes will appear on the printed leaflet

### 8. Addresses

#### Marketing Authorisation holder

Auden Mckenzie (Pharma Division) Ltd, 30 Stadium Business Centre, North End Road, Middlesex, HA9 0AT, UK.

#### Manufacturer

Weimer Pharma GmbH, Im Steingerüst 30, 76437 Rastatt, Germany.

Date of preparation of this leaflet: June 2007

The Parkinson's Disease Society is a charity dedicated to supporting all people with Parkinson's, their families, friends and carers. If you want to get advice, information or support, call their freephone helpline on **0808 800 0303**, Monday to Friday 9:30am to 5:30pm or see their website at [www.parkinsons.org.uk](http://www.parkinsons.org.uk)

**Apomorphine Hydrochloride 10mg/ml Solution for Injection**  
**PL 17507/0051**



AUDEN MCKENZIE (PHARMA DIVISION) LIMITED  
Page 4 of 4

CG817/1

## PATIENT INFORMATION LEAFLET

### Apomorphine Hydrochloride 10mg/ml Solution for Injection

Read this leaflet carefully before this medicine is used. Keep this leaflet; you may want to read it again later. If you have any questions, please ask your doctor or pharmacist (chemist). This medicine has been prescribed for you. It should not be given to anyone else. It may harm them, even if their symptoms are similar to yours.

#### In this leaflet:

- Why do you need to use this medicine?
- How does this medicine work?
- Before you use Apomorphine Hydrochloride 10mg/ml Solution for Injection
- How to use Apomorphine Hydrochloride 10mg/ml Solution for Injection
- Possible side effects
- Storing Apomorphine Hydrochloride 10mg/ml Solution for Injection
- What is in Apomorphine Hydrochloride 10mg/ml Solution for Injection?
- Addresses

#### Apomorphine Hydrochloride 10mg/ml Solution for Injection

### 1. Why do you need to use this medicine?

Apomorphine is used to treat symptoms of Parkinson's disease. It helps 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.

### 2. How does this medicine work?

Apomorphine is one of several medicines known as 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. Dopamine helps in the passing of signals from one nerve cell (neuron) to another. In Parkinson's disease, not enough dopamine is produced by the brain. Dopamine agonists can mimic the effects of dopamine on its target cells in the brain and can provide relief of symptoms of Parkinson's disease.

Despite the name, apomorphine does not contain morphine.

### 3. Before you use Apomorphine Hydrochloride 10mg/ml Solution for Injection

You should not use Apomorphine Hydrochloride 10mg/ml Solution for Injection until you have received thorough training and feel confident to do so.

You should not use Apomorphine Hydrochloride 10mg/ml Solution for Injection;

- if you have difficulty breathing
- if you have liver disease
- if you have dementia such as Alzheimer's disease
- if you are allergic to any of the ingredients of this medicine (see section 7)
- if you have psychiatric problems (such as confusion, hallucinations) or other mental disturbances

CG817/1

Page 1 of 4

- if you have severe dyskinesia (unwanted movements) or dystonia (unusual muscle tone)
- if you are under 18 years of age

Tell your doctor or nurse:

- if you have kidney problems
- if you have breathing difficulties
- if you have heart disease
- if you suffer from nausea and vomiting
- if you have low blood pressure (feel faint or dizzy on standing)
- if you are taking any medicines to treat high or low blood pressure

as he/she may want to take extra care with you, particularly if you are elderly or unwell.

If you are taking levodopa as well as Apomorphine Hydrochloride 10mg/ml Solution for Injection for treatment of your Parkinson's disease, your doctor may want you to have blood tests at regular intervals.

**Pregnancy and Breast feeding**

If you are pregnant, or think you may be, tell your doctor.

You should not breast feed as apomorphine may get into breast milk.

**Driving**

Apomorphine can make you feel sleepy. If you notice that you feel sleepy, you must not drive or do any activity (such as operating machines) where lack of alertness may put you or others at risk of serious injury.

**Other medicines**

Always tell your doctor if you are taking any other medicines or herbal remedies because taking some medicines together can be harmful, including medicines you have bought yourself. Remember that the doctor treating your Parkinson's Disease may not have been informed if you have recently begun a course of treatment for another illness, so please tell him/her.

Some medicines may affect how your body uses apomorphine:

- neuroleptics (a group of medicines used to treat psychiatric problems), e.g. clozapine.

**4. How to use Apomorphine Hydrochloride 10mg/ml Solution for Injection**

**Only to be used for adults, including the elderly.**

**Your doctor or nurse will provide full training and only when you or your carer is confident to perform the injection should treatment be undertaken.**

The dose for each injection and the number of injections required each day will be determined by your personal needs. Your doctor will tell you how much of your medicine you should inject and how often.

The dose for you will have been worked out during your treatment in hospital or at a specialist clinic. The usual dose is typically in the range of 3 to 30 mg, injected 1 to 10 times a day at the first sign of an "off" period. You should inject it under the skin (subcutaneously) on the outside of your thigh or on the lower part of your tummy. **It must not be injected into a vein.**

If you have any concerns about how much to use or where to inject, check with your doctor or nurse.

You may have a **continuous infusion** (a slow injection over a period of time) of apomorphine instead of several single injections. Your doctor or nurse will decide if you need to have Apomorphine Hydrochloride 10mg/ml Solution for Injection in this way. The usual dose is between 1 mg and 4 mg per hour, usually only during waking hours. Your doctor or nurse will decide which dose is best for you and train you to do this. Do not attempt this treatment until you have been trained and are sure what to do.

**Do not use if the solution has turned green. Use only if the solution is clear and colourless.**

Immediately after opening the ampoule, withdraw the required amount of solution into the syringe and then throw away any leftover solution down the toilet.

Used syringes, needles and ampoules should be placed in a "sharps" bin or other puncture-proof container, such as an empty coffee jar. When your "sharps" bin or container is full, please give it to your nurse or doctor for safe disposal – **do not put it in the household rubbish.**

**What to do if you use too many injections**

It is important not to inject more than the prescribed dose. If you inject too much medicine, tell your doctor or contact your nearest hospital emergency department immediately.

**5. Possible side effects**

All medicines sometimes cause side effects in some people. The following side effects of Apomorphine have been reported:

Very Common (affecting more than 10 patients out of 100)

- Lumps under the skin at the site of injection. These can be sore (may even form ulcers), be troublesome and may be itchy. If this problem occurs, your doctor may advise you to vary the site of injection or suggest ultrasound treatment to break-up the lumps.

Common (affecting 1-10 patients out of 100)

- At the start of treatment you may feel very sleepy or fall asleep for a short time after each dose. This usually stops after the first few weeks but if not, contact your doctor. (See section 3 'Driving').
- Feeling sick or being sick - Most patients take a medicine called 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.
- Mild confusion or hallucinations (seeing things differently or things that are not there). These are usually short-lived.

Uncommon (affecting 1-10 patients out of 1,000)

- Low blood pressure (feeling faint or dizzy upon standing up). This is usually short-lived.
- Increased unwanted movements or worsening tremors during 'on' periods.
- Local and generalised rashes.
- Anaemia or blood disorders – a side effect which can occur in patients also taking levodopa (another medicine for the treatment of Parkinson's disease). (See section 3)
- Breathing difficulties

**LABELLING**



Apomorphine Hydrochloride  
20mg in 2ml  
CARTON ONLY

Auden Mckenzie (Pharma Division) Ltd. Artwork Design Department	
Product:	Apomorphine Hydrochloride 10mg/ml
Strength:	20mg in 2ml x 5 ampoules
Colour:	Font: Feb ZCC: Process: Black Color: Gray 6C
Artwork for:	CARTON
Code:	CG649/1
Barcode / EAN No:	5060032240961
Artwork Date:	08.01.07
Version:	1 e
Notes:	Carton artwork only.

Scaling: 1:1

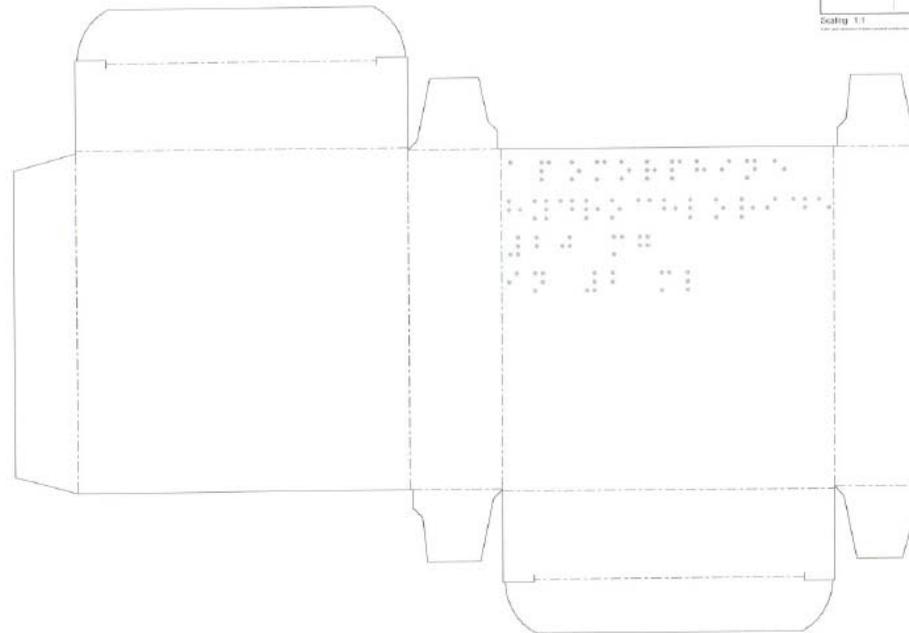




Apomorphine Hydrochloride  
20mg in 2ml  
BRAILLE ONLY

Sandoz - Pfizer Pharma Division Ltd. - Product Design Department		
Product	Apomorphine Hydrochloride 10mg/ml	
Strength	10mg in 2ml - 5 ampoules	
Packaging	Primary	White
	Secondary	White/Black
	Unit of Use	10ml
Material	CA/PC/PC	
Code	014001	
Barcode / EAN	506004240001	
Barcode Date	11.05.09	
Version	1.0	
Notes		

Scaling: 1:1

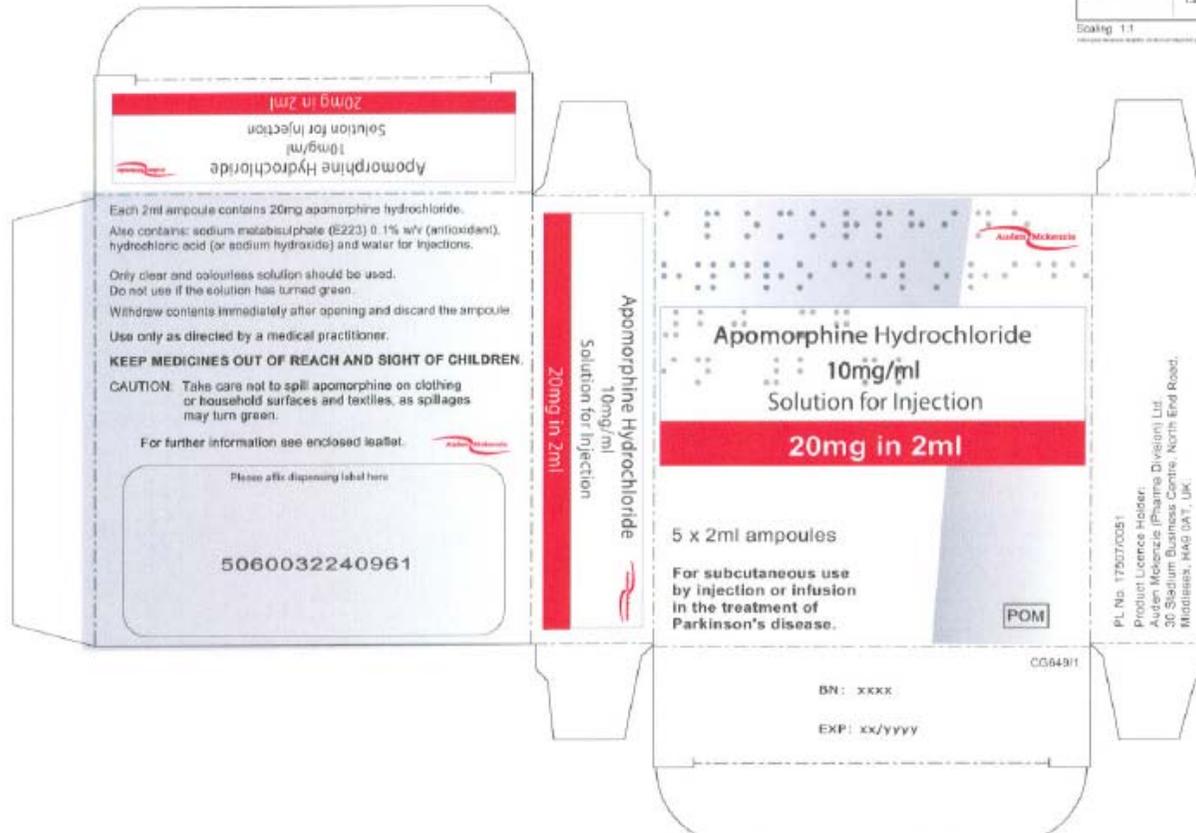


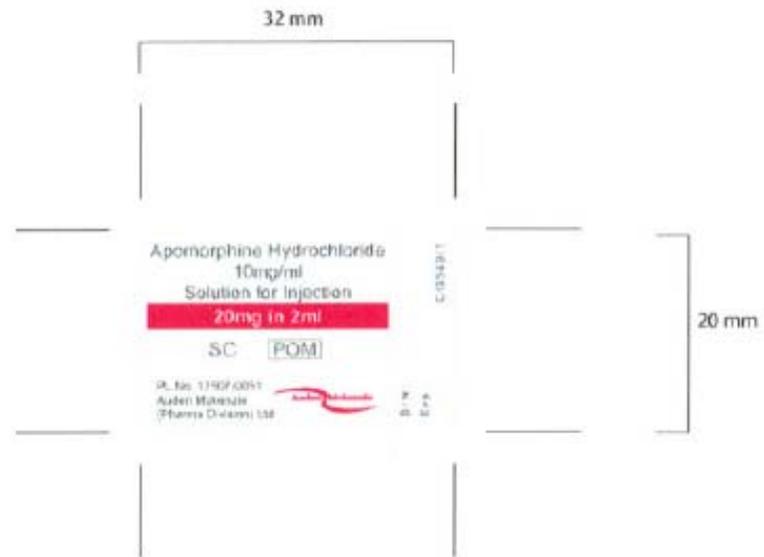


Apomorphine Hydrochloride  
20mg in 2ml  
CARTON & BRAILLE

Title: Mirvaso (Pharma Division) Ltd, Artwork Design Department	
Product:	Apomorphine Hydrochloride 10mg/ml
Strength:	20mg in 2ml / 5 ampoules
Colours:	Inkset 6/3 Z00C Process Black Gold Grey 0C
Artwork ID:	CG649/1
Date:	CG649/1
Barcode / TAIL No:	5060032240961
Artwork Date:	08.03.07
Version:	1.0
Notes:	Carton with inverted Braille impression...

Scaling: 1:1  
© 2007 Auden Mckenzie (Pharma Division) Ltd





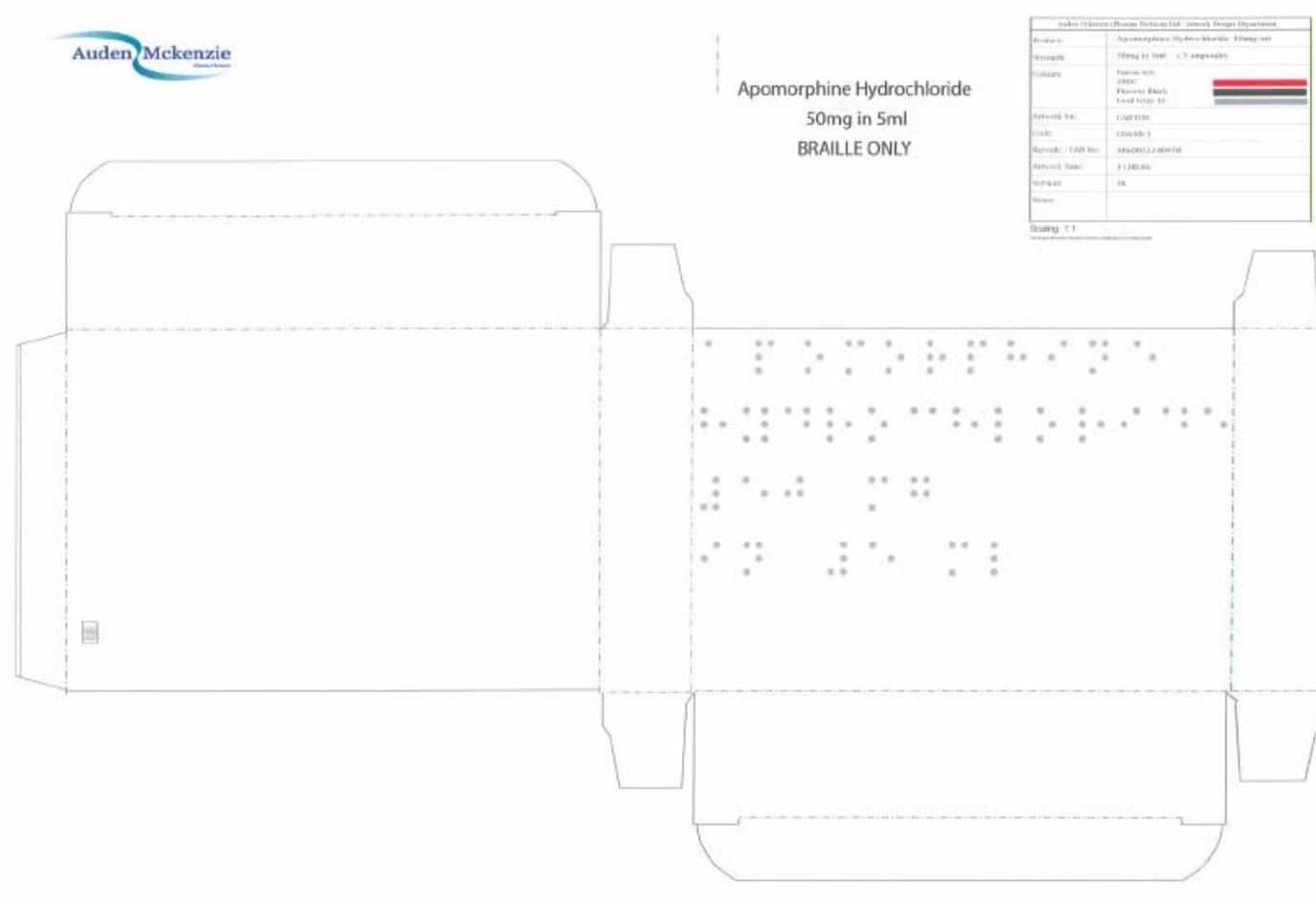


Apomorphine Hydrochloride  
50mg in 5ml  
CARTON ONLY

Auden Mckenzie (Pharma Division) Ltd. Artwork Design Department	
Product:	Apomorphine Hydrochloride 10mg/ml
Strength:	50mg in 5ml x 5 ampoules
Colours:	process red: 200C: Process Black: Cool Gray 6C:
Artwork for:	CARTON
Code:	CQ050/1
Barcode / EAN No.:	5060032240978
Artwork Date:	08.01.07
Version:	1.c
Notes:	Carton artwork only.

Scaling: 1:1  
Colour separations should be made on a professional printing press







Apomorphine Hydrochloride  
50mg in 5ml  
CARTON & BRAILLE

Auden Mckenzie (Pharma Division) Ltd. - Technical Design Department	
Product:	Apomorphine Hydrochloride 10mg/ml
Strength:	50mg in 5ml x 5 ampoules
Colours:	Font colour: ZIRC Process: Black Coat: Gray, CC
Artwork Ref:	CMETON
Code:	CT-0030/1
Barcode / EAN No.:	50600032240978
Artwork Date:	08.01.07
Version:	1
Notes:	Carton with overlaid braille impression...

Scaling: 1:1  
© 2007 Auden Mckenzie (Pharma Division) Ltd.

50mg in 5ml

Apomorphine Hydrochloride  
10mg/ml  
Solution for Injection

Each 5ml ampoule contains 50mg apomorphine hydrochloride.  
Also contains: sodium metabisulphate (E223) 0.1% w/v (antioxidant), hydrochloric acid (or sodium hydroxide) and water for injections.

Only clear and colourless solution should be used. Do not use if the solution has turned green.  
Withdraw contents immediately after opening and discard the ampoule.

**KEEP MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.**

Use only as directed by a medical practitioner.

**CAUTION:** Take care not to spill apomorphine on clothing or household surfaces and textiles, as spillages may turn green.

For further information see enclosed leaflet.

Please affix dispensing label here

5060032240978

Apomorphine Hydrochloride  
10mg/ml  
Solution for Injection  
50mg in 5ml

Apomorphine Hydrochloride  
10mg/ml  
Solution for Injection

50mg in 5ml

5 x 5ml ampoules

**For subcutaneous use by injection or infusion in the treatment of Parkinson's disease.**

POM

CG859/1

BN: xxxx

EXP: xx/yyyy

PL No. 17507/0051  
Product Licence Holder:  
Auden Mckenzie (Pharma Division) Ltd,  
30 Stadium Business Centre, North End Road,  
Middlesbrough, Middlesbrough, Cleveland, North Yorkshire, YO21 2DA, UK

