DIAMORPHINE HYDROCHLORIDE BP 100 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

DIAMORPHINE HYDROCHLORIDE BP 500 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

PL 30956/0001-2

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DIAMORPHINE HYDROCHLORIDE BP 100 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

DIAMORPHINE HYDROCHLORIDE BP 500 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

PL 30956/0001-2

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Diamorphine Hydrochloride BP 100 mg Lyophilisate for Solution for Injection and Diamorphine Hydrochloride BP 500 mg Lyophilisate for Solution for Injection (product licence numbers: 30956/0001-2).

Diamorphine Hydrochloride BP Lyophilisate for Solution for Injection is used to help to relieve pain. It can be used to relieve pain associated with surgery, a heart attack or a terminal illness, or to relieve breathlessness caused by fluid in the lungs.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Diamorphine Hydrochloride BP Lyophilisate for Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.

DIAMORPHINE HYDROCHLORIDE BP 100 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

DIAMORPHINE HYDROCHLORIDE BP 500 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

PL 30956/0001-2

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Auralis marketing authorisations for the medicinal products Diamorphine Hydrochloride BP 100 mg Lyophilisate for Solution for Injection and Diamorphine Hydrochloride BP 500 mg Lyophilisate for Solution for Injection (PL 30956/0001-2) on 12 February 2008. These medicines are available only on prescription.

Diamorphine is a narcotic analgesic which acts primarily on the central nervous system and smooth muscle. Diamorphine may be used in the treatment of severe pain associated with surgical procedures, myocardial infarction or pain in the terminally ill, and for the relief of dyspnoea in acute pulmonary oedema.

These standard abridged applications are for solutions for injection containing 100mg or 500mg of diamorphine hydrochloride. The applications are made under Article 10a of Directive 2001/83/EC, as amended., demonstrating the well-established use of this kind of product.

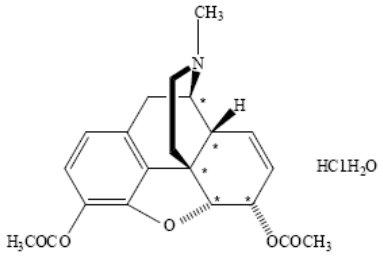
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Diamorphine hydrochloride

Chemical Names: 4,5-Epoxy-17-methylmorphinan-3,6-diyldiacetate hydrochloride monohydrate
(5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate (ester)

CAS Registry Numbers: 1502-95-0 Diamorphine hydrochloride
561-27-3 Diamorphine base



Diamorphine hydrochloride contains 5 chiral centres (*).

Molecular Formula: $C_{21}H_{23}NO_5.HCl.H_2O$

Molecular Weight: Diamorphine base 369.4
Diamorphine hydrochloride anhydrous 405.9
Diamorphine hydrochloride monohydrate 423.9

Physical form: A white or almost white crystalline powder; odourless when freshly prepared but develops an odour characteristic of acetic acid on storage.

Solubility: Water 1 part in 1.6
Chloroform 1 part in 1.6
Ethanol 1 part in 12
Ether almost insoluble

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

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

Active diamorphine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

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

Appropriate stability data have been generated supporting a retest period of 4 years, with no specific storage instructions.

DRUG PRODUCT

Other ingredients

This product consists solely of the drug substance, diamorphine hydrochloride.

No overages are used in the finished product.

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

Product is packaged in 5 ml clear Ph. Eur. Class 1 glass ampoules containing either 100 mg or 500 mg diamorphine hydrochloride BP lyophilisate. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. The ampoules are packed into a carton of five.

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. Storage conditions are “Store below 25ºC”, “Protect from light”, “Keep container in the outer carton” and “For storage conditions of the reconstituted medicinal product, see section 6.3.” (section 6.3 of the SPC states “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 – 8 °C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.” These storage conditions are appropriate for a product of this type.

Bioequivalence / Bioavailability

No bioequivalence study has been performed as this is an injectable formulation which is acceptable.

Essential Similarity

The applications were submitted as bibliographic applications and are not claiming essential similarity to the brand leader.

Assessor’s Overall Conclusions

The applications are considered approvable.

PRECLINICAL ASSESSMENT

No preclinical studies were performed with this product, which is considered to be acceptable given that these applications are for a product containing a well-established active substance. The applicant has submitted appropriate published literature references.

CLINICAL ASSESSMENT

INDICATIONS

The applicant has submitted the following:

"Diamorphine may be used in the treatment of severe pain associated with surgical procedures, myocardial infarction or pain in the terminally ill and for the relief of dyspnoea in acute pulmonary oedema."

These are consistent with the established indications for diamorphine and are satisfactory.

DOSE & DOSE SCHEDULE

The applicant has submitted the following:

"Diamorphine may be given by the intramuscular, intravenous or subcutaneous routes. Glucose intravenous infusion is the preferred diluent, particularly when the drug is administered by a continuous infusion pump over 24 to 48 hours, although it is also compatible with sodium chloride intravenous infusion.
The dose should be suited to the individual patient.
Adults:
Acute pain, 5 mg repeated every four hours if necessary (up to 10 mg for heavier, well muscled patients) by subcutaneous or intramuscular injection. By slow intravenous injection, one quarter to one half the corresponding intramuscular dose.
Chronic pain, 5-10 mg regularly every four hours by subcutaneous or intramuscular injection. The dose may be increased according to individual needs.
Myocardial infarction, 5 mg by slow intravenous injection (1 mg/minute) followed by a further 2.5 mg to 5 mg if necessary.
Acute pulmonary oedema, 2.5 mg to 5 mg by slow intravenous injection (1mg/minute).
If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection of diamorphine equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*— absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).
To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
If treatment continues for more than 24 hours it may be appropriate to use a syringe driver (Burne R, Hunt A, Palliative Medicine 1987, 1, 27-30)

Children and Elderly:
Diamorphine has been used in the treatment of terminally ill children. Diamorphine has been administered in reduced doses to children with neoplastic disease when it becomes difficult to give treatment orally. The starting dose should be selected according to age, size, symptoms and previous analgesic requirements and administered 4 hourly; the dose being titrated according to the degree of pain.
As diamorphine has a respiratory depressant effect, care should be taken when giving the drug to the very young and the elderly and a lower starting dose than normal is recommended.

Patients with hepatic or renal dysfunction:
Diamorphine undergoes biotransformation to an active metabolite, morphine-6-glucuronide (M6G). This metabolite can accumulate and result in greater pharmacological effect, because it is more active than morphine. Less diamorphine will therefore be needed. Care needs to be taken with unconscious intensive care patients on fixed dose schedules where their renal function is impaired.
A wide range of doses of diamorphine can be given intravenously or subcutaneously starting with the "standard" 5-10mg regularly every four hours recommended in the SmPC. Lower starting doses are recommended for patients with hepatic or renal impairment. Ultimately, the dose given to the individual is arrived at by titrating to therapeutic effect."

These are largely consistent with the dose schedules for other diamorphine products and are satisfactory.

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.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PATIENT INFORMATION LEAFLET (PIL)
The PIL reflects the SPC and is satisfactory. It was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

LABELLING
The labelling text conforms to statutory requirements and is medically satisfactory.

APPLICATION FORM (MAA)
The MAA is medically satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC for this product is in line with that

MEDICAL CONCLUSION
A marketing authorisation may be granted for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Diamorphine Hydrochloride BP 100 mg and 500 mg Lyophilisate for 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 preclinical studies were performed with this product, which is considered to be acceptable given that these applications are for a product containing a well-established active substance. The applicant has submitted appropriate published literature references.

EFFICACY AND SAFETY

The efficacy of diamorphine hydrochloride has been well documented in the past. No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been demonstrated for Diamorphine Hydrochloride BP 100 mg and 500 mg Lyophilisate for Solution for Injection in the therapeutic indications proposed. The risk benefit is therefore considered to be positive.

DIAMORPHINE HYDROCHLORIDE BP 100 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

DIAMORPHINE HYDROCHLORIDE BP 500 MG LYOPHILISATE FOR SOLUTION FOR INJECTION

PL 30956/0001-2

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 14 February 2007
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15 May 2007
3	Following assessment of the application the MHRA requested further information on the quality dossier on 3 July 2007. The applicant responded to the MHRA's requests, providing further information on 20 July 2007.
4	The MHRA requested further information on the clinical dossier on 4 September 2007. The applicant responded to the MHRA's requests, providing further information on 11 September 2007.
5	The MHRA requested further information on the quality dossier on 3 January 2008. The applicant responded to the MHRA's requests, providing further information on 16 January 2008.
6	The MHRA requested further information on the quality dossier on 29 January 2008. The applicant responded to the MHRA's requests, providing further information on 30 January 2008.
7	The MHRA requested further information on the quality dossier on 6 February 2008. The applicant responded to the MHRA's requests, providing further information on 7 February 2008.
8	The application was determined on 12 February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

PL 30956/0001:

1 NAME OF THE MEDICINAL PRODUCT

Diamorphine Hydrochloride BP 100 mg Lyophilisate for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 100 mg of Diamorphine Hydrochloride BP.

3 PHARMACEUTICAL FORM

Lyophilisate for solution for injection.

A white to off-white, sterile, freeze dried powder of Diamorphine Hydrochloride BP
for reconstitution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diamorphine may be used in the treatment of severe pain associated with surgical procedures, myocardial infarction or pain in the terminally ill and for the relief of dyspnoea in acute pulmonary oedema.

4.2 Posology and method of administration

Diamorphine may be given by the intramuscular, intravenous or subcutaneous routes. Glucose intravenous infusion is the preferred diluent, particularly when the drug is administered by a continuous infusion pump over 24 to 48 hours, although it is also compatible with sodium chloride intravenous infusion.
The dose should be suited to the individual patient.
Adults:
Acute pain, 5 mg repeated every four hours if necessary (up to 10 mg for heavier, well muscled patients) by subcutaneous or intramuscular injection. By slow intravenous injection, one quarter to one half the corresponding intramuscular dose.
Chronic pain, 5-10 mg regularly every four hours by subcutaneous or intramuscular injection. The dose may be increased according to individual needs.
Myocardial infarction, 5 mg by slow intravenous injection (1 mg/minute) followed by a further 2.5 mg to 5 mg if necessary.
Acute pulmonary oedema, 2.5 mg to 5 mg by slow intravenous injection (1mg/minute).
If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection of diamorphine equivalent to one-sixth of the total 24-hour

subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).
To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
If treatment continues for more than 24 hours it may be appropriate to use a syringe driver (Burne R, Hunt A, Palliative Medicine 1987, 1, 27-30)

Children and Elderly:
Diamorphine has been used in the treatment of terminally ill children. Diamorphine has been administered in reduced doses to children with neoplastic disease when it becomes difficult to give treatment orally. The starting dose should be selected according to age, size, symptoms and previous analgesic requirements and administered 4 hourly; the dose being titrated according to the degree of pain.
As diamorphine has a respiratory depressant effect, care should be taken when giving the drug to the very young and the elderly and a lower starting dose than normal is recommended.

Patients with hepatic or renal dysfunction:
Diamorphine undergoes biotransformation to an active metabolite, morphine-6- glucuronide (M6G). This metabolite can accumulate and result in greater pharmacological effect, because it is more active than morphine. Less diamorphine will therefore be needed. Care needs to be taken with unconscious intensive care patients on fixed dose schedules where their renal function is impaired.
A wide range of doses of diamorphine can be given intravenously or subcutaneously starting with the "standard" 5-10mg regularly every four hours recommended in the SmPC. Lower starting doses are recommended for patients with hepatic or renal impairment. Ultimately, the dose given to the individual is arrived at by "titrating to therapeutic effect".
Instructions for use and handling
Instructions for preparation: see Section 6.6.
Further advice on use and handling can be found in the current British National Formulary (BNF/BNFC) (*Prescribing in Palliative Care and Syringe Drivers*).

4.3 Contraindications

Respiratory depression and obstructive airways disease.
Phaeochromocytoma (endogenous release of histamine may stimulate catecholamine release).
Raised intracranial pressure.
Concurrent use of monoamine oxidase inhibitors or within two weeks of their discontinuation.

4.4 Special warnings and precautions for use

Diamorphine should be administered with care to patients with head injuries as there is an increased risk of respiratory depression which may lead to elevation

of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
Repeated administration of diamorphine may lead to dependence and tolerance developing. Abrupt withdrawal in patients who have developed dependence may precipitate a withdrawal syndrome. Great caution should be exercised in patients with a known tendency or history of drug abuse.
Use with caution in patients with toxic psychosis, CNS depression, myxoedema, prostatic hypertrophy or urethral stricture, kyphoscoliosis, acute alcoholism, delirium tremens, severe inflammatory or obstructive bowel disorders, adrenal insufficiency or severe diarrhoea. Care should be exercised in treating the elderly or debilitated patients and those with hepatic or renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

The depressant effects of diamorphine may be exaggerated and prolonged by phenothiazines, monoamine oxidase inhibitors, tricyclic antidepressants, anxiolytics and hypnotics. There may be antagonism of the gastrointestinal effects of cisapride, domperidone and metoclopramide. The risk of severe constipation and/or urinary retention is increased by administration of antimuscarinic drugs (e.g. atropine). There may be increased risk of toxicity with 4-quinolone antibacterials.
Alcohol may enhance the sedative and hypotensive effects of diamorphine.
Cimetidine inhibits metabolism of opioid analgesics.
Hyperpyrexia and CNS toxicity have been reported when opioid analgesics are used with selegiline.

4.6 Pregnancy and lactation

Safety has not been established in pregnancy.
Administration during labour may cause respiratory depression in the neonate and gastric stasis during labour, increasing the risk of inhalation pneumonia.
Diamorphine should not be given to women who are breast-feeding as there is limited information available on diamorphine in breast milk.

4.7 Effects on ability to drive and use machines

Diamorphine causes drowsiness and mental clouding. If affected patients should not drive or use machines.

4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression although circulatory depression is also possible. The most common side effects are sedation, nausea and vomiting, constipation and sweating. Other side effects include dizziness, miosis, confusion, urinary retention, biliary spasm, orthostatic hypotension, facial flushing, vertigo, palpitations, mood changes, dry mouth, dependence, urticaria, pruritus and raised intracranial pressure.

4.9 Overdose

a) Symptoms
Respiratory depression, pulmonary oedema, muscle flaccidity, coma or stupor, constricted pupils, cold, clammy skin and occasionally bradycardia and hypotension.

b) Treatment
Respiration and circulation should be maintained and naloxone is indicated if coma or bradypnoea are present. A dose of 0.4 to 2 mg repeated at intervals of two to three minutes (up to 10 mg) may be given by subcutaneous, intramuscular or intravenous injection. The usual initial dosage for children is 10 micrograms per kg body weight. Naloxone may also be given by continuous intravenous infusion, 2 mg diluted in 500 ml, at a rate adjusted to the patient's response. Oxygen and assisted ventilation should be administered if necessary.

5 PHARMACOLOGICAL PROPERTIES

ATC code: NO2AA09

5.1 Pharmacodynamic properties

Diamorphine is a narcotic analgesic which acts primarily on the central nervous system and smooth muscle. It is predominantly a central nervous system depressant but it has stimulant actions resulting in nausea, vomiting and miosis.

5.2 Pharmacokinetic properties

Diamorphine is a potent opiate analgesic which has a more rapid onset of activity than morphine as the first metabolite, monoacetylmorphine, more readily crosses the blood brain barrier. In man, diamorphine has a half life of two to three minutes. Its first metabolite, monoacetylmorphine, is more slowly hydrolysed in the blood to be concentrated mainly in skeletal muscle, kidney, lung, liver and spleen. Monoacetylmorphine is metabolised to morphine. Morphine forms conjugates with glucuronic acid. The majority of the drug is excreted via the kidney as glucuronides and to a much lesser extent as morphine. About 7-10 % is eliminated via the biliary system into the faeces. Diamorphine does not bind to protein. However, morphine is about 35 % bound to human plasma proteins, mainly to albumin. The analgesic effect lasts approximately three to four hours.

5.3 Preclinical safety data

There are no additional pre-clinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

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 – 8 °C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25ºC. Protect from light.
Keep container in the outer carton.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml clear Ph. Eur. Class 1 glass ampoules containing 100 mg Diamorphine Hydrochloride BP lyophilisate each.
The ampoules are packed into a carton of 5.

6.6 Special precautions for disposal

The product is prepared by dissolving Diamorphine Hydrochloride Lyophilisate for Solution for Injection in the requisite amount of water for injection immediately before use.
The reconstituted lyophilisate is a clear solution.
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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.
Continuous subcutaneous infusion should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Auralis
Daresbury Innovation Centre,
Keckwick Lane, Daresbury, Halton WA4 4FS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30956/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/02/2008

10 DATE OF REVISION OF THE TEXT

12/02/2008

PL 30956/0002:

1 NAME OF THE MEDICINAL PRODUCT

Diamorphine Hydrochloride BP 500 mg Lyophilisate for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 500 mg of Diamorphine Hydrochloride BP.

3 PHARMACEUTICAL FORM

Lyophilisate for solution for injection.

A white to off-white, sterile, freeze dried powder of Diamorphine Hydrochloride BP for reconstitution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diamorphine may be used in the treatment of severe pain associated with surgical procedures, myocardial infarction or pain in the terminally ill and for the relief of dyspnoea in acute pulmonary oedema.

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To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
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4.3 Contraindications
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Phaeochromocytoma (endogenous release of histamine may stimulate catecholamine release).
Raised intracranial pressure.
Concurrent use of monoamine oxidase inhibitors or within two weeks of their discontinuation.

4.4 Special warnings and precautions for use
Diamorphine should be administered with care to patients with head injuries as there is an increased risk of respiratory depression which may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
Repeated administration of diamorphine may lead to dependence and tolerance developing. Abrupt withdrawal in patients who have developed dependence

may precipitate a withdrawal syndrome. Great caution should be exercised in patients with a known tendency or history of drug abuse.
Use with caution in patients with toxic psychosis, CNS depression, myxoedema, prostatic hypertrophy or urethral stricture, kyphoscoliosis, acute alcoholism, delirium tremens, severe inflammatory or obstructive bowel disorders, adrenal insufficiency or severe diarrhoea. Care should be exercised in treating the elderly or debilitated patients and those with hepatic or renal impairment.

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Administration during labour may cause respiratory depression in the neonate and gastric stasis during labour, increasing the risk of inhalation pneumonia.
Diamorphine should not be given to women who are breast-feeding as there is limited information available on diamorphine in breast milk.

4.7 Effects on ability to drive and use machines

Diamorphine causes drowsiness and mental clouding. If affected patients should not drive or use machines.

4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression although circulatory depression is also possible. The most common side effects are sedation, nausea and vomiting, constipation and sweating. Other side effects include dizziness, miosis, confusion, urinary retention, biliary spasm, orthostatic hypotension, facial flushing, vertigo, palpitations, mood changes, dry mouth, dependence, urticaria, pruritus and raised intracranial pressure.

4.9 Overdose

a) Symptoms
Respiratory depression, pulmonary oedema, muscle flaccidity, coma or stupor, constricted pupils, cold, clammy skin and occasionally bradycardia and hypotension.
b) Treatment
Respiration and circulation should be maintained and naloxone is indicated if coma or bradypnoea are present. A dose of 0.4 to 2 mg repeated at intervals of two to three minutes (up to 10 mg) may be given by subcutaneous,

intramuscular or intravenous injection. The usual initial dosage for children is 10 micrograms per kg body weight. Naloxone may also be given by continuous intravenous infusion, 2 mg diluted in 500 ml, at a rate adjusted to the patient's response. Oxygen and assisted ventilation should be administered if necessary.

5 PHARMACOLOGICAL PROPERTIES

ATC code: NO2AA09

5.1 Pharmacodynamic properties

Diamorphine is a narcotic analgesic which acts primarily on the central nervous system and smooth muscle. It is predominantly a central nervous system depressant but it has stimulant actions resulting in nausea, vomiting and miosis.

5.2 Pharmacokinetic properties

Diamorphine is a potent opiate analgesic which has a more rapid onset of activity than morphine as the first metabolite, monoacetylmorphine, more readily crosses the blood brain barrier. In man, diamorphine has a half life of two to three minutes. Its first metabolite, monoacetylmorphine, is more slowly hydrolysed in the blood to be concentrated mainly in skeletal muscle, kidney, lung, liver and spleen. Monoacetylmorphine is metabolised to morphine. Morphine forms conjugates with glucuronic acid. The majority of the drug is excreted via the kidney as glucuronides and to a much lesser extent as morphine. About 7-10 % is eliminated via the biliary system into the faeces. Diamorphine does not bind to protein. However, morphine is about 35 % bound to human plasma proteins, mainly to albumin. The analgesic effect lasts approximately three to four hours.

5.3 Preclinical safety data

There are no additional pre-clinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

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 – 8 °C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25ºC. Protect from light.
Keep container in the outer carton.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml clear Ph. Eur. Class I glass ampoules containing 500 mg Diamorphine Hydrochloride BP lyophilisate each.
The ampoules are packed into a carton of 5.

6.6 Special precautions for disposal

The product is prepared by dissolving Diamorphine Hydrochloride Lyophilisate for Solution for Injection in the requisite amount of water for injection immediately before use.
The reconstituted lyophilisate is a clear solution.
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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.
Continuous subcutaneous infusion should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Auralis
Daresbury Innovation Centre,
Keckwick Lane, Daresbury, Halton WA4 4FS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30956/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/02/2008

10 DATE OF REVISION OF THE TEXT

12/02/2008

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Diamorphine Hydrochloride BP 100 mg and 500 mg Lyophilisate for Solution for Injection

Read all of this leaflet carefully, before you are given this injection.

- Keep this leaflet. You may need to read it again.
- If you have any other questions, please ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Before being used, the powder in the ampoules will be mixed with a liquid to make a solution which will be given to you by injection. This is called Diamorphine Hydrochloride BP Injection in this leaflet.

1. WHAT DIAMORPHINE HYDROCHLORIDE BP INJECTION IS AND WHAT IT IS USED FOR

Diamorphine hydrochloride belongs to a class of medicines known as opioid analgesics. They help to relieve pain.

Diamorphine Hydrochloride BP Injection can be used to

- relieve severe pain associated with surgery, a heart attack or a terminal illness, or
- relieve breathlessness caused by fluid in the lungs.

2. BEFORE DIAMORPHINE HYDROCHLORIDE BP INJECTION IS GIVEN TO YOU

Diamorphine Hydrochloride BP Injection is not suitable for everyone. Tell the doctor or nurse that you must not have the injection if:

- you are aware that you are allergic to diamorphine or any other opioid analgesic such as codeine
- you have a tumour of the adrenal gland near your kidney
- you have severe problems with breathing or suffer from bronchitis or asthma
- you have raised pressure in your brain
- you have recently been treated for depression with drugs called monoamine oxidase inhibitors (MAOIs)
- you are pregnant or breast-feeding.

Before having the injection make sure your doctor is aware if:

- you are ill or elderly
- you have problems with your liver or kidneys
- you have a head injury
- you are an alcoholic or have a history of drug abuse
- you have a mental illness
- you have problems with your thyroid, adrenal glands, prostate, bladder or bowel
- you have diarrhoea
- you have a severely deformed spine.

Are you taking other medicines?

Before the doctor gives you the injection tell him/her if you are taking any of the following medicines:

- Drugs to treat depression or mental illness including phenothiazines or tricyclic antidepressants as well as monoamine oxidase inhibitors
- Tranquillisers or sleeping tablets
- Antimuscarinic drugs such as atropine
- Drugs to prevent vomiting such as metoclopramide or domperidone
- Cisapride which is used to stimulate the gut
- Selegiline, a drug used in Parkinson's disease
- An antibiotic called a 4-quinolone
- Cimetidine, used to treat stomach ulcers and indigestion, or if
- You have been drinking alcohol.

Make sure you tell your doctor about any other medicines you are taking, or have taken recently, including any bought from a chemist or another shop.

Pregnancy and childbirth

- If you are given diamorphine during pregnancy, there is a risk that your baby might become dependant on it and suffer from withdrawal symptoms after birth.
- If you are given diamorphine during labour there is a risk that you could be sick and have breathing difficulties, or the baby could have difficulty starting to breathe.

Driving and using machines

The injection may cause drowsiness and loss of concentration so you should not operate a machine or drive a vehicle.

3. HOW THE INJECTION IS GIVEN

The doctor will prepare the injection by mixing the powder with a liquid. He/she will know how much to give you. You can have the injection either under the skin, or into a muscle, or directly into a vein (called intravenous infusion).

The usual doses for adults are:

To relieve pain 5 - 10 mg every 4 hours injected under the skin or into a muscle.

If the drug is given directly into a vein, you will be given one quarter or one half of this dose.

The dose may be increased if necessary.

Following a heart attack 5 mg directly into a vein, followed, if needed, by a further 2.5 - 5 mg.

For fluid in the lungs 2.5 - 5 mg directly into a vein.

The elderly, children or people with liver or kidney problems, may be given a lower starting dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diamorphine Hydrochloride BP Injection may cause side effects in a few people.

The most serious side effect is that your breathing or circulation may become depressed. Your breathing may become shallow or you may collapse.

The most common side effects are drowsiness, feeling or being sick, constipation and sweating.

Other side-effects, which may occur, include dizziness, constricted pupils (eye), confusion, difficulty in passing water, spasm of the bile duct, feeling faint on standing up, facial flushing, palpitations, mood changes, dry mouth, skin rash, itching and headache.

If you have the injections for a long time you might become dependent on the drug and have withdrawal symptoms if it is suddenly stopped.

If you experience any other side-effects or feel that the medicine is affecting you badly, tell your doctor or nurse immediately.

5. STORING THE INJECTION

- Do not store above 25ºC. Keep the injection in the outer carton to protect it from light.
- This medicine should not be used after the expiry date on the carton or if the powder in the ampoule or the solution are discoloured.
- Diamorphine Hydrochloride BP Injection must be used immediately after the solution has been prepared.
- Diamorphine Hydrochloride BP Injection must be kept in a secure place out of the reach and sight of children.
- Diamorphine Hydrochloride BP is a Controlled Drug and must be stored and disposed of according to regulations.

6. FURTHER INFORMATION

Each 5 ml ampoule contains either 100 mg or 500 mg of the active ingredient, Diamorphine Hydrochloride BP, which is a white or off-white powder. The medicine is prepared for use by dissolving the powder in a liquid.

Each pack contains 5 glass ampoules.

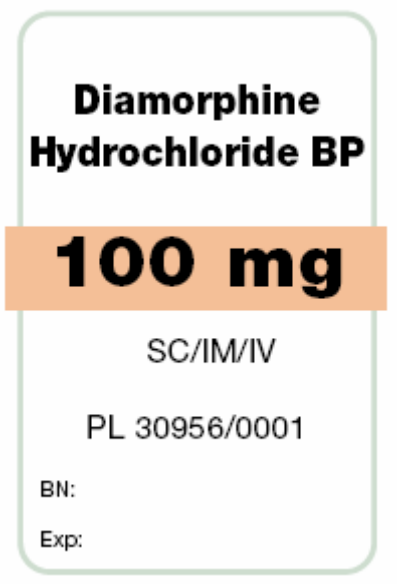
The Marketing Authorisation Holder and Manufacturer is Auralis, Daresbury Innovation Centre, Keckwick Lane, Daresbury, Halton WA4 4FS, United Kingdom.

This leaflet was prepared in November 2006. For any more information about this medicine, or to obtain the leaflet in a different format please contact the Marketing Authorisation Holder 01925 607071.

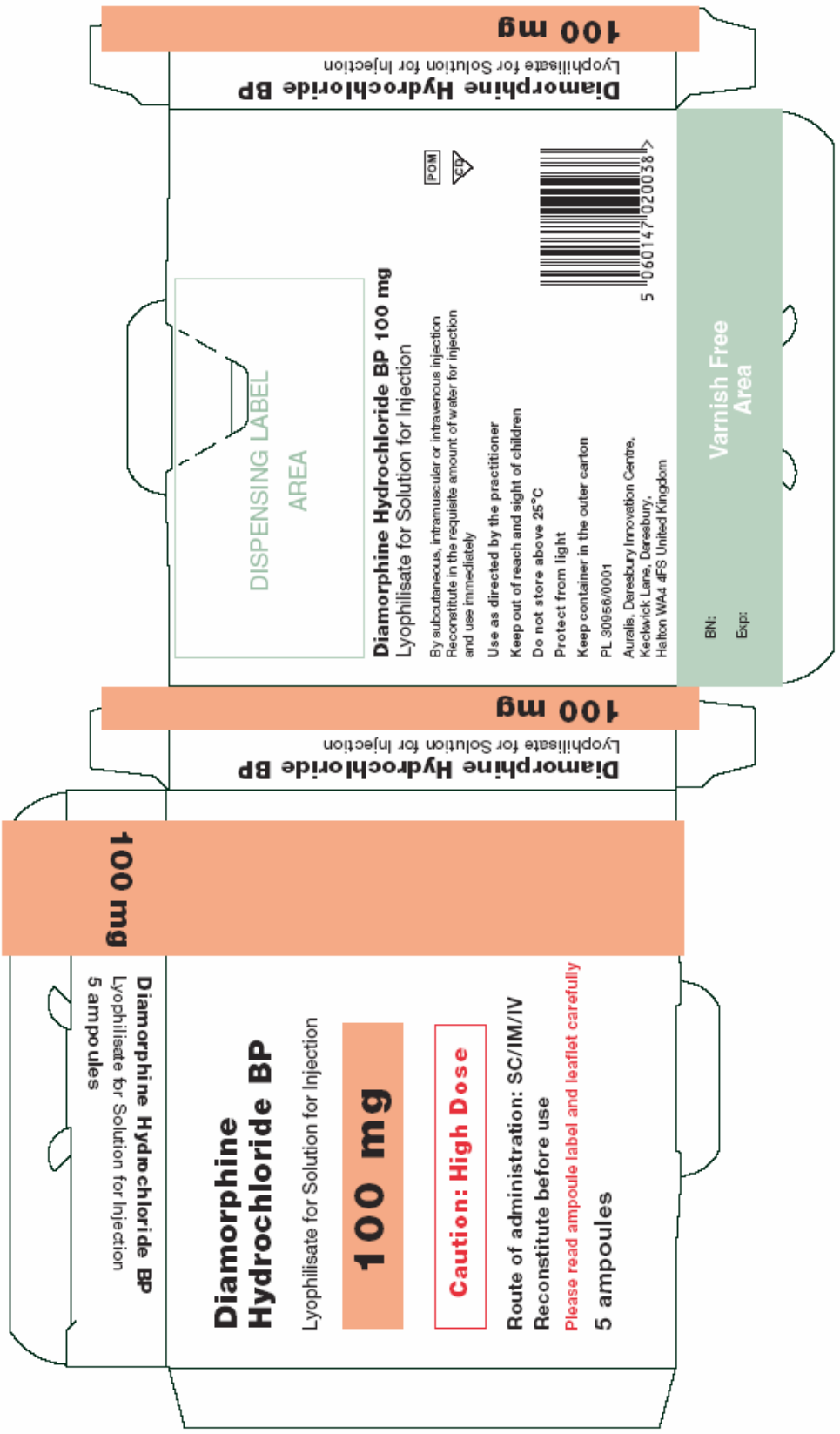
LABELLING

PL 30956/0001:

Ampoule label



Carton


100 mg
Diamorphine Hydrochloride BP
Lyophilisate for Solution for Injection
Diamorphine Hydrochloride BP
Lyophilisate for Solution for Injection
5 ampoules
Diamorphine Hydrochloride BP
Lyophilisate for Solution for Injection
100 mg
Caution: High Dose
Route of administration: SC/IM/IV
Reconstitute before use
Please read ampoule label and leaflet carefully
5 ampoules
100 mg
Diamorphine Hydrochloride BP
Lyophilisate for Solution for Injection
DISPENSING LABEL AREA
Diamorphine Hydrochloride BP 100 mg
Lyophilisate for Solution for Injection
By subcutaneous, intramuscular or intravenous injection
Reconstitute in the requisite amount of water for injection
and use immediately
Use as directed by the practitioner
Keep out of reach and sight of children
Do not store above 25°C
Protect from light
Keep container in the outer carton
PL 30956/0001
Aurelia, Daresbury Innovation Centre,
Keckwick Lane, Daresbury,
Halton WA4 4FS United Kingdom
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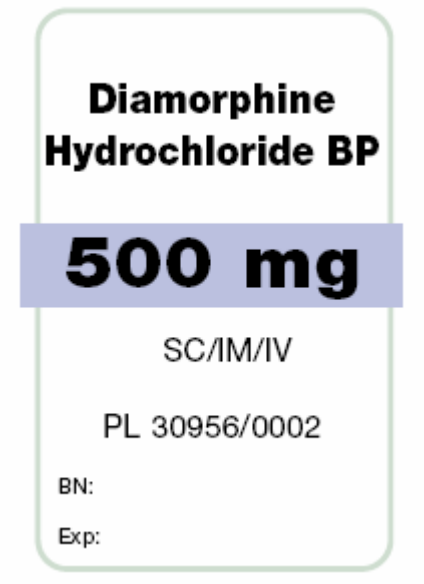
BN:
Exp:
Varnish Free Area

PL 30956/0002:

Ampoule label



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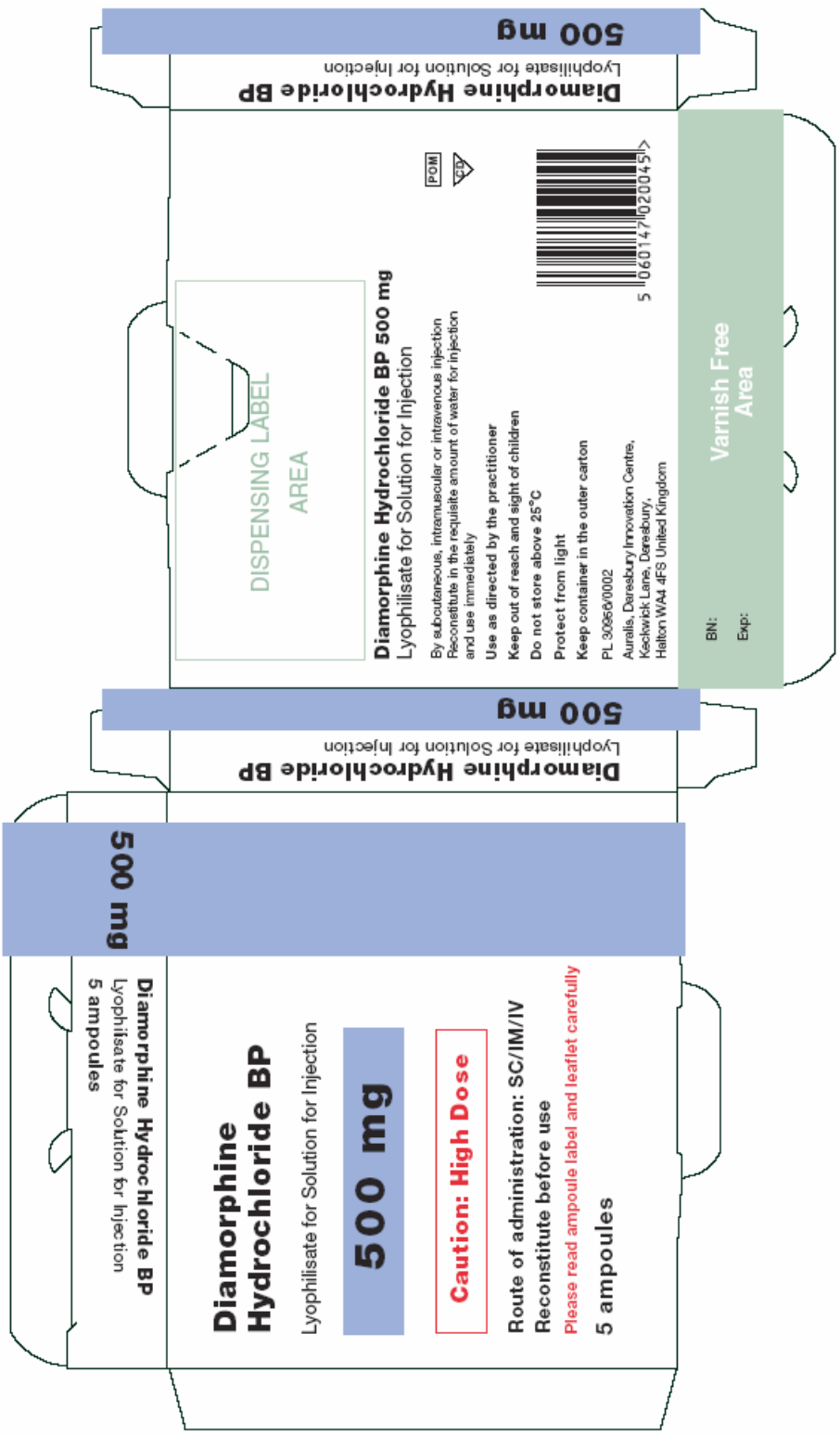
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