# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Diamorphine Hydrochloride 100mg For Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diamorphine Hydrochloride 100mg.

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

A freeze dried powder, which when in aqueous solution is suitable for parenteral administration.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

As an analgesic in terminal care.

### 4.2 Posology and method of administration

Method of administration

By intramuscular, subcutaneous or intravenous injection, the latter 2 routes using either bolus injection or infusion. 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.

Posology

It is important that dosage be suited to the individual patient, taking into account the properties of the drug, the nature of the pain, the total condition of the patient and previous or concurrent medication.

Adults: Cancer: Use of diamorphine or other narcotic analgesics although very important, should be only one part of the comprehensive approach to total pain control, which ideally should include non-drug measures and psycho-social support. Diamorphine may be used parenterally when oral administration of narcotic analgesics is no longer possible because of the dosage required, impaired absorption, intestinal disorders, nausea and vomiting or difficulty in swallowing.

An initial dosage of 5 to 10mg every 4 hours may be suitable, but higher doses are reported in the literature (Dover SB, BMJ 1987, 294, 553-555). The initial dosage will usually depend on the doses and drugs given previously.

Persistent pain is controlled by titrating the dose against the degree of pain, until the smallest dose required to remove the pain is reached. This dose is maintained and the patient's condition continually reassessed, the dose being increased or decreased as necessary. The therapeutic objective must be to control the pain by regular administration of the correct dose when this is determined, and continuous infusion may be preferred to intermittent therapy.

**Equivalent Doses of Morphine Sulphate by mouth (as oral solution or standard tablets or as modified-release tablets) or of Diamorphine Hydrochloride by Intramuscular Injection or by Subcutaneous Infusion:**

These equivalences are approximate only and may need to be adjusted according to response:

| ORAL MORPHINE | | PARENTERAL MORPHINE | |
|---|---|---|---|
| Morphine sulphate oral solution or standard tablets | Morphine sulphate modified release tablets | Diamorphine hydrochloride by intramuscular injection | Diamorphine hydrochloride by subcutaneous infusion |
| **every 4 hours** | **every 12 hours** | **every 4 hours** | **every 24 hours** |

| | | | |
|---|---|---|---|
| 5mg | 20mg | 2.5mg | 15mg |
| 10mg | 30mg | 5mg | 20mg |
| 15mg | 50mg | 5mg | 30mg |
| 20mg | 60mg | 7.5mg | 45mg |
| 30mg | 90mg | 10mg | 60mg |
| 40mg | 120mg | 15mg | 90mg |
| 60mg | 180mg | 20mg | 120mg |
| 80mg | 240mg | 30mg | 180mg |
| 100mg | 300mg | 40mg | 240mg |
| 130mg | 400mg | 50mg | 300mg |
| 160mg | 500mg | 60mg | 360mg |
| 200mg | 600mg | 70mg | 400mg |

Elderly: Mainly because of its respiratory depressant effect caution should be exercised when giving the drug to the elderly and a reduced dose should be used.

Children: 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. If treatment continues for more than 24 hours it may be appropriate to use a syringe driver.

Hepatic impairment:
A reduction in dosage should be considered in hepatic impairment.

Renal impairment:
The dosage should be reduced in moderate to severe renal impairment.

Debilitated patients:
A reduction in dosage should be considered in debilitated patients.

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use.

Discontinuation of therapy

An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to

discontinuation. Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with diamorphine hydrochloride in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in

section 6.1.

Acute respiratory depression, obstructive airways disease. Concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of treatment with them.

Biliary Colic (see also biliary tract disorders, 4.4 Special Warnings and Precautions).

Phaeochromocytoma (endogenous release of histamine may stimulate catecholamine release).

Coma. Raised intracranial pressure. Head injuries, as there is an increased risk of respiratory depression that may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient

Acute alcoholism.

Diamorphine is also contra-indicated where there is a risk of paralytic ileus, or in acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated)

## 4.4 Special warnings and precautions for use

Morphine-like opioids should either be avoided in patients with biliary tract disorders or they should be given with an antispasmodic (use in biliary colic is a contraindication see 4.3 Contraindications)

Diamorphine should be given in reduced doses or with caution to patients with asthma or decreased respiratory reserve (including kyphoscoliosis, emphysema, severe obesity, cor pulmonale). Avoid use during an acute asthma attack (see 4.3 Contraindications).

Care should be exercised in treating the elderly, children, debilitated patients, and those with hepatic or renal impairment (see 4.2 Posology for dosage recommendations). It is recommended that a lower than normal initial dose is given to these patients. Administration to patients with head injuries or raised intracranial pressure increases the risk of respiratory depression and further elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient. The drug can cause hypotension in patients who already have conditions or drug therapy that interfere with the ability to maintain normal blood pressure. Careful consideration, or use in reduced doses, should be given before treating patients with myxoedema or hypothyroidism, adrenocortical insufficiency, toxic psychosis, CNS depression, prostatic hypertrophy or urethral stricture, kyphoscoliosis, acute alcoholism and delirium tremens, severe inflammatory or obstructive bowel disorders, hypotension, shock, convulsive disorders, adrenal insufficiency or debilitated patients and severe diarrhoea.

Palliative care - in the control of pain in terminal illness, these conditions should not necessarily be a deterrent to use.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Diamorphine and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Diamorphine concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Morphine has an abuse potential similar to other strong agonist opioids, and should be used with particular caution in patients with a history of alcohol or drug abuse.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with

current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine.

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with diamorphine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Diamorphine. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Diamorphine may result in overdose and/or

death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

## 4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

The concomitant use of Diamorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Concurrent administration of other CNS sedative/hypnotic drugs may have an addictive effect necessitating their dosage reduction. Concomitant administration of Diamorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Alcohol: Alcohol may enhance the sedative and hypotensive effects of diamorphine.

Anti-arrhythmics: Diamorphine may delay the absorption of mexiletine.
Antidepressants, anxiolytics, hypnotics: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concomitant use of monoamine oxidase inhibitors (MAOIs) and pethidine. It is therefore possible that a similar interaction may occur with other opioid analgesics - avoid concomitant use and for two weeks after stopping MAOIs.

The depressant effects of diamorphine may be exaggerated and prolonged by tricyclic antidepressants, anxiolytics and hypnotics.

Antivirals: Plasma concentration of opioid analgesics (except methadone) is possibly increased by ritonavir. Opioids potentiate the effects of CNS depressants including tricyclic antidepressants, anxiolytics and hypnotics.

Antipsychotics: enhanced sedative and hypotensive effect.

Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin): concurrent use may increase the risk of severe constipation.

Antimuscarinics: The risk of severe constipation and/or urinary retention is increased by administration of antimuscarinic drugs (e.g. atropine).

Motility stimulants: There may be antagonism of the gastrointestinal effects of domperidone and metoclopramide.

Cimetidine inhibits metabolism of opioid analgesics.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as diamorphine may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

## 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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - o It was not affecting your ability to drive safely.

## 4.8 Undesirable effects

The most serious hazards of therapy are respiratory depression and arrest, although circulatory depression, shock and cardiac arrest can occur.

The most common side-effects are: sedation, nausea and vomiting, constipation and sweating. Tolerance generally develops with long-term use, but not to constipation.

Other side-effects include:

Anaphylaxis: Anaphylactic reactions following intravenous injection have been reported rarely.

Disorders of the eye: blurred or double vision or other changes in vision, miosis.

Nervous system disorders:

*frequency unknown*: allodynia, hyperalgesia (see section 4.4), hyperhidrosis, faintness and syncope, euphoria, dysphoria, weakness, insomnia, dizziness, vertigo, headache, mood changes including dysphoria and euphoria, mental clouding, confusional symptoms and occasionally hallucinations

Immune system disorders:

*frequency unknown:* anaphylactoid reactions

Gastrointestinal disorders:

*frequency unknown*: dry mouth, anorexia, cramps, taste alterations, biliary spasm.

Psychiatric disorders:

*frequency unknown*: drug dependence (see Section 4.4)

General disorders and administration site:

*frequency unknown*: drug withdrawal (abstinence) syndrome

Cardiac disorders:

frequency unknown: tachycardia, bradycardia, palpitations

Vascular disorders:

*frequency unknown*: postural hypotension, orthostatic hypotension, facial flushing

Renal and urinary disorders:

*frequency unknown*: urinary retention, difficulty with micturition, ureteric spasm, antidiuretic effect. Tolerance develops to the effects of opioids on the bladder.

Sexual dysfunction:

*frequency unknown*: long term use may lead to a reversible decrease in libido or potency

Skin and subcutaneous tissue disorders:

*frequency unknown*: pruritus, urticaria and other skin rashes

Drug withdrawal symptoms:

Dysphoric mood, anxiety have also been reported.

Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see 4.4.

Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, “drug craving” is often involved.

Drug dependence

Repeated use of Diamorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store.

## 4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms

The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts.

Other opioid overdose symptoms include cold, clammy skin, hypotension, bradycardia, circulatory failure, muscle flaccidity, severe weakness, severe

nervousness or restlessness, confusion, severe dizziness, severe drowsiness, hallucinations, convulsions (especially in infants and children), rhabdomyolysis progressing to renal failure

Management

Respiration and circulation should be maintained.

The specific antidote naloxone is indicated if coma or bradypnoea are present. A dose of 0.4 to 2mg may be given by s.c., i.m. or i.v. injection repeated at intervals of 2-3 minutes up to a maximum of 10mg if respiratory function does not improve. The dosage for children is 10 micrograms per kilogram body weight. Alternatively, naloxone may be given by continuous i.v. infusion; 2mg diluted in 500ml intravenous solution, at a rate adjusted to the patient's response. Oxygen and assisted ventilation should be administered if necessary.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Nervous System Drugs, Drugs used in opioid dependence, ATC code: N07BC06

Diamorphine is a narcotic analgesic obtained from opium which acts mainly 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. It can provoke the release of endogenous histamine and thereby induce catecholamine release.

## 5.2 Pharmacokinetic properties

| | |
|---|---|
| Absorption: | Rapidly and completely absorbed after oral administration or by injection, absorption from the gastro-intestinal tract may be erratic. |
| Blood concentration: | In cases of fatal overdose, the total morphine concentrations of 100 to 900ng/ml have been detected. |
| Half life: | Range 1.7 - 5.3 minutes, mean 3 minutes, active metabolites 2 - 3 hours. |
| Distribution: | The diamorphine metabolites, morphine and 6-monoacetylmorphine, rapidly cross the blood brain barrier. Morphine crosses the placenta and is secreted in the milk. 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 |
| Metabolic reactions: | Rapidly hydrolysed to 6-monoacetylmorphine which is further hydrolysed to morphine. Normorphine is also formed, all metabolites may be conjugated with glucuronic acid, morphine may be conjugated at positions 3 or 6. |
| Excretion: | Up to 80% of a dose is recovered in the urine in 24 hours, after oral or parenteral administration, most of the dose is recovered as morphine-3-glucuronide with about 5 to 7% as free morphine, 1% as 6-monoacetylmorphine, 0.1% as unchanged drug and trace amounts of the other metabolites. |

### 5.3 Preclinical safety data

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for Injection BP - not detectable

### 6.2 Incompatibilities

Diamorphine is incompatible with mineral acids and alkalis.
Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store below 25ºC. Protect from light.

### 6.5 Nature and contents of container

Five 5ml type 1 neutral glass ampoules contained in a printed tamper evident cardboard carton.

### 6.6 Special precautions for disposal

Reconstitute in 1ml of 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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

## 7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,
Unit G4,
Riverside Industrial

Estate, Riverside Way,
Dartford,
DA1 5BS UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0011

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/02/2001

## 10 DATE OF REVISION OF THE TEXT

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