SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morphine Martindale 10 mg/ml
Morphine Martindale 20 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine Martindale 10 mg/ml

Each 1 ml of solution contains 10 mg of morphine sulfate.

Excipients with known effect:

Also, contains 3.26 mg of sodium per ml and sodium metabisulphite.

Morphine Martindale 20 mg/ml

Each 1 ml of solution contains 20 mg of morphine sulfate.

Excipients with known effect:

Also, contains 2.74 mg of sodium per ml and sodium metabisulphite.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.
A clear**,** colourless or almost colourless, particle free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery.

Pre-operatively as an adjunct to anesthesia for pain relief and to allay anxiety. Alleviation of the anxiety associated with severe pain. It is useful as a hypnotic where sleeplessness is due to pain.

4.2 Posology and method of administration

Posology

Adults

Subcutaneous or Intramuscular Injection

The usual dose by subcutaneous or intramuscular injection is 5-20 mg every 4 hours.

Intravenous Injection

Doses of up to 15 mg have been given by slow intravenous injection, sometimes as a loading dose for continuous or patient-controlled infusion.

Elderly

Because of the depressant effect on respiration, caution is necessary when giving morphine to the elderly. A reduction of dose is advisable.

Hepatic Impairment

Morphine may precipitate coma in hepatic impairment – avoid or reduce dose.

Renal Impairment

A reduced maintenance dose may be necessary in moderate to severe impairment.

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.

Method of administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Morphine Injection is intended for intramuscular, intravenous and subcutaneous administration.

The subcutaneous route is not suitable for oedematous patients.

Notes:

1. Resuscitative equipment and medications, including a specific antagonist (naloxone HCl injection) should be immediately available for management of respiratory depression or other complications that may arise from inadvertent morphine intravascular administration. Also, facilities for adequate monitoring of the patient's respiratory status must be available for 24 hours after each dose since delayed respiratory depression may occur.

2. Rapid I.V. injection of most opioid analgesics has caused chest wall rigidity, anaphylactoid reactions, severe respiratory depression, hypotension, peripheral circulatory collapse and cardiac arrest.

The patient usually should be lying down and should remain recumbent for a period of time to minimize side effects such as hypotension, dizziness, lightheadedness, nausea and vomiting. If these side effects occur in an ambulatory patient, they may be relieved if the patient lies down. An opioid antagonist and equipment for artificial ventilation should be available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute respiratory depression
- Asthma attack or Chronic Obstructive Airways Disease
- Acute alcoholism
- Biliary colic (see section 4.4)
- Head injuries, comatose patients or increased intracranial pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
- Heart failure secondary to lung disease
- Monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal
- Risk of paralytic ileus
- Phaeochromocytoma (due to the risk of pressor response to histamine release)

- Acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated)
- Morphine is contraindicated in premature infants or during labor for delivery of a premature infant

4.4 Special warnings and precautions for use

Repeated use can cause tolerance and dependence. Caution in use should be exercised and a reduction in dose may be advisable in the elderly and in the following cases:

- Hypotension
- Hypothyroidism
- Depressed respiratory reserve
- Prostatic hypertrophy
- Hepatic or renal impairment (avoid or reduce dose)
- Convulsive disorders
- Asthma (avoid during attack)
- Adrenocortical insufficiency
- Urethral stricture
- Inflammatory or obstructive bowel disorders

Opioids such as morphine should either be avoided in patients with biliary disorders or they should be given with an antispasmodic. Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi. Therefore, in patients with biliary tract disorders morphine may exacerbate pain (use in biliary colic is a contraindication, see 4.3).

In patients given morphine after cholecystectomy, biliary pain has been induced. Abrupt withdrawal from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose and the duration of drug use. Great caution should be exercised in patients with a known tendency or history of drug abuse.

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

<u>Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:</u>

Concomitant use of Morphine Sulfate 1mg/ml Solution for Injection 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 Morphine Sulfate 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).

<u>Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)</u>

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 that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

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.

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. For individual symptoms, see section 4.8.

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.

Morphine Martindale contains sodium

Morphine Martindale 10 mg/ml

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Morphine Martindale 20 mg/ml

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Oral P2Y12 inhibitor antiplatelet therapy

Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced sedative and hypertensive effects.

Anti-arrhythmics: There may be delayed absorption of mexiletine.

Antibacterials: The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided.

Antidepressants, anxiolytics, hypnotics: Severe CNS excitation or depression (hypertension or hypotension) has been reported with the concurrent use of pethidine and monoamine oxidase inhibitors (MAOIs) including selegiline, moclobemide and linezolid. As it is possible that a similar interaction may occur with other opioid analgesics, morphine should be used with caution and consideration given to a reduction in dosage in patients receiving MAOIs.

The sedative effects of morphine (opioid analgesics) are enhanced when used with depressants of the central nervous system such as hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

Antipsychotics: possible enhanced sedative and hypotensive effect.

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

Antimuscarinics**:** agents such as atropine antagonise morphine-induced respiratory depression and can partially reverse biliary spasm but are additive to the gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive antimuscarinic analgesic therapy.

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

Oral P2Y12 inhibitor antiplatelet therapy

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Morphine sulfate should only be used when benefit is known to outweigh risk. As with all drugs it is not advisable to administer morphine during pregnancy. Morphine crosses the placental barrier. Administration during labour may cause respiratory depression in the

new born infant and gastric stasis during labour, increasing the risk of inhalation pneumonia. Therefore, it is not advisable to administer morphine during labour.

Babies born to opioid-dependent mothers may suffer withdrawal symptoms including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms including yawning, sneezing, mottling and fever.

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome.
Treatment may include an opioid and supportive care.

Breast-feeding:
While morphine can suppress lactation, the quantity from therapeutic doses that may reach the neonate via breast milk is probably insufficient to cause major problems of dependence or adverse effects.

Fertility:
Animal studies have shown that morphine may reduce fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Morphine causes drowsiness so patients should avoid driving or operating machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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

4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression (see section 4.9). The commonest side-effects of morphine are

- Nausea
- Vomiting
- Constipation
- Drowsiness
- Dizziness

Tolerance generally develops with long term use, but not to constipation. Other side effects include the following:

Psychiatric disorders

- Dependence

Immune system disorders:

- Anaphylactic reactions following intravenous injection have been reported rarely, anaphylactoid reactions

Cardiac disorders:

- Bradycardia
- Palpitations
- Tachycardia
- Orthostatic hypotension

Nervous system disorders:
- Myoclonus
- Mental clouding
- Confusion (with large doses)
- Hallucinations
- Headache
- Vertigo
- Mood changes including dysphoria
- Euphoria
- Allodynia
- Hyperalgesia (see section 4.4)
- Hyperhidrosis

Gastrointestinal disorders:
- Dry mouth
- Biliary spasm

Eye disorders:
- Blurred or double vision or other changes in vision
- Miosis

Reproductive system and breast disorders:
- Long term use may lead to a reversible decrease in libido or potency

Skin and subcutaneous tissue disorders:
- Pruritus
- Urticaria
- Rash
- Sweating
- Contact dermatitis has been reported and pain and irritation may occur on injection.
- Facial flushing

Musculoskeletal and connective tissue disorders
- Muscle rigidity

Renal and urinary disorders:
- Difficulty with micturition
- Ureteric spasm
- Urinary retention
- Antidiuretic effect

General disorders and administration site conditions:
- Drug withdrawal (abstinence) syndrome

Tolerance develops to the effects of opioids on the bladder.

The euphoric activity of morphine has led to its abuse and physical and psychological dependence may occur (see section 4.4).

Description of selected adverse reactions
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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose
Toxic doses vary considerably with the individual, and regular users may tolerate large doses.

The triad of respiratory depression, coma and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops. Death may occur from respiratory failure.

Other opioid overdose symptoms include hypothermia, confusion, severe dizziness, severe drowsiness, hypotension, bradycardia, circulatory failure pulmonary oedema, severe nervousness or restlessness, hallucinations, pneumonia aspiration, convulsions (especially in infants and children).
Rhabdomyolysis, progressing to renal failure, has been reported in overdosage.

Death may occur from respiratory failure
Treatment: The medical management of overdose involves prompt administration of the specific opioid antagonist naloxone if coma or bradypnoea are present using one of the recommended dosage regimens. Both respiratory and cardiovascular support should be given where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium

alkaloids, ATC Code: N02AA01

Morphine is a narcotic analgesic obtained from opium, which acts mainly on the central nervous system and smooth muscle.

Morphine is a potent analgesic with competitive agonist actions at the μ-receptor, which is thought to mediate many of its other actions of respiratory depression, euphoria, inhibition of gut motility and physical dependence. It is possible that analgesia, euphoria and dependence may be due to the effects of morphine on a μ-1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on a μ-2 receptor subtype.

Morphine is also a competitive agonist at the κ-receptor that mediates spinal analgesia, miosis and sedation. Morphine has no significant actions at the other two major opioid receptors, the δ- and the σ-receptors.
Morphine directly suppresses cough by an effect on the cough centre in the medulla. Morphine also produces nausea and vomiting by directly stimulating the chemoreceptor trigger zone in the area postrema of the medulla. Morphine provokes the release of histamine.

5.2 Pharmacokinetic properties Absorption:
Variably absorbed after oral administration; rapidly absorbed after subcutaneous or intramuscular administration.

Blood concentration: After an oral dose of 10 mg as the sulfate, peak serum concentrations of free morphine of about 10 ng/ml are attained in 15 to 60 minutes; after an intramuscular does of 10 mg, peak serum concentrations of 70 to 80 ng/ml are attained in 10 to 20 minutes; after an intravenous does of 10 mg, serum concentrations of about 60 ng/ml are obtained in 15 minutes falling to 30 ng/ml after 30 minutes and to 10 ng/ml after 3 hours; subcutaneous doses give similar concentrations to intramuscular doses at 15 minutes but remain slightly higher during the following 3 hours; serum concentrations measured soon after administration correlate closely with the ages of the subjects studied and are increased in the aged.

Half-life:
Serum half-life in the period 10 minutes to 6 hours following intravenous administration, 2 to 3 hours; serum half-life in the period 6 hours onwards, 10 to 44 hours.

Distribution:
Widely distributed throughout the body, mainly in the kidneys, liver, lungs and spleen; lower concentrations appear in the brain and muscles; morphine crosses the placenta and traces are secreted in sweat and milk; protein binding, about 35% bound to albumin and to

immunoglobulins at concentrations within the therapeutic range.

Biotransformation:
Mainly glucuronic acid conjugation to form morphine-3 and 6-glucuronides, with sulfate conjugation. N-demethylation, 0-methylation and N-oxide glucuronide formation occurs in the intestinal mucosa and liver; N-demethylation occurs to a greater extent after oral than parenteral administration; the 0-methylation pathway to form codeine has been challenged and codeine and norcodeine metabolites in urine may be formed from codeine impurities in the morphine sample studied.

Elimination:
After an oral dose, about 60% is excreted in the urine in 24 hours, with about 3% excreted as free morphine in 48 hours; after parenteral dose, about 90% is excreted in 24 hours, with about 10% as free morphine, 65 to 70% as conjugated morphine, 1% as normorphine and 3% as normorphine glucuronide; after administration of large doses to addicts about 0.1% of a dose is excreted as norcodeine; urinary excretion of morphine appears to be pH dependent to some extent: as the urine becomes more acid more free morphine is excreted and as the urine becomes more alkaline more of the glucuronide conjugate is excreted; up to 10% of a dose may be excreted in the bile.

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
Sodium chloride,
Sodium metabisulfite,
Water for injection.
The pH may be adjusted with sodium hydroxide or sulfuric acid solution.

6.2 Incompatibilities
Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities (sometimes attributed to particular formulations) have included aciclovir sodium, doxorubicin, fluorouracil, frusemide, heparin sodium, pethidine hydrochloride, promethazine hydrochloride and tetracyclines. Specialised references should be consulted for specific compatibility information.
Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulfate and 5-fluorouracil.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear, colourless 1ml Ph.Eur type1 glass ampoules containing sufficient solution to permit the removal of 1 ml. 10 ampoules are packed into a cardboard carton.

6.6 Special precautions for disposal and other handling

Any solution remaining should be discarded or returned to the pharmacy.

7. MANUFACTURER

Macarthys Laboratories Ltd t/a Martindale Pharmaceuticals, Bampton Road, Harold Hill, Romford, RM3 8UG, UK

8. REGISTRATION HOLDER

MBI Pharma Ltd. P.O.B 5061, Kadima

9. MARKETING AUTHORISATION NUMBERS

Morphine Martindale 10 mg/ml: 163-86-35125

Morphine Martindale 20 mg/ml: 163-87-35126

Approved in November 2020.