SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

M.I.R. 15

M.I.R. 30

2. Qualitative and quantitative composition

M.I.R. 15: Each tablet contains Morphine Sulfate 15 mg

M.I.R. 30: Each tablet contains Morphine Sulfate 30 mg

Excipients with known effect (**M.I.R. 15** and **M.I.R. 30)**: Lactose
Excipients with known effect (**M.I.R. 30):** Azorubine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Immediate release tablets

M.I.R. 15
Blue, scored tablets

M.I.R. 30

Pink, scored tablets

4. Clinical particulars

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see sections 4.4, 4.5].
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

M.I.R. tablets are indicated for the relief of moderate to severe pain.

4.2 Posology and method of administration

Route of administration
Oral.

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

Adults and children over 12 years:
The dosage of **M.I.R.** tablets is dependent on the severity of pain and the patient's previous history of analgesic requirements. One tablet to be taken every four to six hours or as directed by a physician. Increasing severity of pain or tolerance to morphine will require increased dosage of **M.I.R.** tablets alone or in combination to achieve the desired relief.

Patients receiving **M.I.R.** tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for any reduction in analgesic effects associated with oral administration. Usually such increased requirement is of the order of 100%. In such patients individual dose adjustments are required.

Elderly:
A reduction in adult dosage may be advisable.
Children 3 -12 years of age:
0.2-0.5 mg/kg/dose every 4-6 hours as needed.

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.

4.3 Contraindications

Morphine products are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe chronic obstructive pulmonary disease
- Severe bronchial asthma
- Severe respiratory depression with hypoxia and/or hypercapnia
- Paralytic ileus
- Acute abdomen
- Head injury
- Delayed gastric emptying
- Known morphine sensitivity
- Acute hepatic disease
- Concurrent administration of mono-amine oxidase inhibitors or within two weeks of discontinuation of their use

Not recommended during pregnancy.
Not recommended for children below 3 years of age.

4.4 Special warnings and precautions for use

M.I.R. tablets should be administered in caution in patients with:

- Impaired respiratory function
- Respiratory depression (see below)
- Severe cor pulmonale
- Sleep apnoea
- CNS depressant co-administration (see below and section 4.5)
- Opioid Use Disorder
- Acute alcoholism
- Delirium tremens
- Head Injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Hypotension with hypovolaemia
- Hypothyroidism

- Adrenocortical insufficiency
- Convulsive disorders
- Biliary tract disorders
- Pancreatitis
- Prostatic hypertrophy
- Inflammatory bowel disorders
- Severely impaired renal function
- Severely impaired hepatic function
- Constipation

As with all narcotics a reduction in dosage may be advisable in the elderly.

M.I.R. tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, **M.I.R.** tablets should be discontinued immediately.

Respiratory Depression
The major risk of opioid excess is respiratory depression.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

Severe cutaneous adverse reactions (SCARs)

Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.
If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

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

Concomitant use of **M.I.R.** tablets 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 **M.I.R.** tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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).

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.

M.I.R. 15 and **M.I.R. 30** tablets contain Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

M.I.R. 30 tablets contain azorubine, which may cause allergic reactions.

Patients about to undergo additional pain-relieving procedures (e.g. surgery, plexus blockade) should not receive **M.I.R.** tablets for 4 hours prior to the intervention. If further treatment with **M.I.R.** tablets is indicated then the dosage should be adjusted to new post-operative requirements. **M.I.R.** tablets should be used with caution pre-operatively and within the first 24 hours post-operatively. **M.I.R.** tablets should also be used with caution following abdominal surgery as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as M.I.R tablets.
Repeated use of M.I.R tablets can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of M.I.R tablets 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).
Before initiating treatment with M.I.R tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.
Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 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.

Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Patients with diseases of the biliary tract should be monitored for worsening of symptoms while administering morphine.

Drug withdrawal syndrome

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 morphine.

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.

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.

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.

Some changes that can be seen with long-term use of opioid analgesics include an increase in serum prolactin, and decreases in plasma cortisol, oestrogen and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Clinical symptoms include decreased libido, impotence or amenorrhea which may be manifested from these hormonal changes.

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.

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)

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

4.5 Interaction with other medicinal products and other forms of interaction

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 dosage and duration of concomitant use should be limited (see section 4.4).

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants, which include, but are not limited to: other opioids, anxiolytics, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids, e.g., pregabalin), general anaesthetics (including barbiturates), antipsychotics (including phenothiazines),other tranquilisers, antidepressants, gabapentin, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

In a study involving healthy volunteers (N = 12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increase by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsons and anti-emetics, may interact with morphine to potentiate the anticholinergic adverse effects.

Cimetidine inhibits the metabolism of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis. Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Plasma concentrations of morphine may be reduced by rifampicin (see section 4.4).

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.

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine, and may possibly decrease plasma concentrations of morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy

M.I.R. tablets are not recommended during pregnancy and labor. Regular use in 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 pregnant women, 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.

Breastfeeding

Administration to nursing women is not recommended as morphine is 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

Treatment with **M.I.R.** tablets may cause sedation and it is not recommended that patients drive or use machines if they experience drowsiness.

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

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with **M.I.R.** tablets but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

The following frequencies are the basis for assessing undesirable effects:
Very common (≥1/10);
Common (≥ 1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000);
Not known (cannot be estimated from the available data).

	Very Common	Common	Uncommon	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Drug dependence (see section 4.4) Dysphoria Thinking disturbances
Nervous system disorders		Dizziness Headache Hyperhidrosis Involuntary muscle contractions Somnolence	Convulsions Hypertonia Myoclonus Paraesthesia Syncope	Allodynia Hyperalgesia (see section 4.4)
Eye disorders			Visual impairment	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory thoracic and mediastinal disorders			Bronchospasm Pulmonary oedema Respiratory depression	Cough decreased Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Dry mouth Vomiting	Dyspepsia Ileus Taste perversion	Pancreatitis
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders		Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders		Asthenia	Peripheral oedema	Drug tolerance

and administration site conditions		Fatigue Malaise Pruritus	Drug withdrawal syndrome	Drug withdrawal (abstinence) syndrome neonatal

Drug dependence and withdrawal (abstinence) syndrome
Repeated use of **M.I.R** tablets 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.
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

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.

Signs of morphine toxicity and overdose are pin-point pupils, skeletal muscle flaccidity, bradycardia, hypotension, respiratory depression, pneumonia aspiration, somnolence and central nervous system depression which can progress to stupor or coma. Death may occur from respiratory failure. Circulatory failure and deepening coma may occur in more severe cases. Overdose can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.

Toxic leukoencephalopathy has been observed with morphine overdose.

Treatment of morphine overdose

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Oral activated charcoal (50g for adults, 1g/kg for children) may be considered if a substantial amount has been ingested within one hour, provided the airway can be protected.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid

ATC code: N02A A01

Morphine acts as an agonist at opiate receptors in the CNS particularly mu and to a lesser extent kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis and sedation.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). Morphine produces respiratory depression by direct action on brain stem respiratory centers.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts. Morphine may produce spasm of the sphincter of Oddi, thus raising intrabiliary pressure.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may affect the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal system resulting in adrenal insufficiency or hypogonadism respectively (see section 4.4).

Hepatobiliary system

Opioids may induce spasm of the sphincter of Oddi (see section 4.4).

Other Pharmacological Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

5.2 Pharmacokinetic properties
Morphine is well absorbed from **M.I.R.** tablets, however first pass metabolism does occur. Apart from the liver, metabolism also occurs in the kidney and intestinal mucosa. The major urinary metabolite is morphine-3-glucuronide but morphine-6-glucuronide is also formed. The half-life for morphine in the plasma is approximately 2.5 - 3.0 hours.

5.3 Preclinical safety data
In male rats, reduced fertility and chromosomal damage in gametes have been reported. There are no other pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

M.I.R. 15: Lactose, corn starch, talc, povidone K25, magnesium stearate**,** indigotine blue (E132)**.**

Each tablet contains approximately 168 mg of lactose.

M.I.R. 30: Lactose, corn starch, talc, povidone K25, magnesium stearate**,** azorubine (E122).

Each tablet contains approximately 153 mg of lactose.

6.2 Incompatibilities
None known.

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

6.4 Special precautions for storage
Store below 25^0C.

6.5 Nature and contents of container
PVC/Aluminum blisters, packs of 20 tablets.

6.6 Special precautions for disposal and other handling
None.

7. Marketing authorisation numbers:

M.I.R. 15: 033-83-25309

M.I.R. 30: 033-84-25310

8. Marketing registration holder:

Rafa Laboratories Ltd. POB 405, Jerusalem 9100301, Israel.

9. Date of revision of the text:

Revised in August 2024.