1. Name of the medicinal product

MCR® 10, MCR® 30, MCR® 100

Controlled release tablets.

For oral use.

2. Qualitative and quantitative composition

Each tablet contains:

MCR 10: Morphine Sulfate 10 mg

MCR 30: Morphine Sulfate 30 mg

MCR 100: Morphine Sulfate 100 mg

Excipients with known effect:

MCR 10 and MCR 30 tablets contain Lactose.

MCR 30 tablets contain sunset yellow (E110).

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Controlled-release tablets

MCR 10 tablets are brown round coated tablets.

MCR 30 tablets are purple round coated tablets.

MCR 100 tablets are grey round coated 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

Prolonged relief of severe pain.

4.2 Posology and method of administration

For the correct and effective use of morphine it is critical to adjust the dosing regimen for each patient individually. The following dosage recommendations are, therefore, only suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

The dosage of morphine is individualized according to the severity of the pain, the patient's age and metabolism, previous history of analgesic therapy, and response to morphine.

The correct dosage for any individual patient is that which is sufficient to control pain with no, or tolerable, side effects for a full 12 hours.

MCR should be taken on a regular 12-hourly schedule, at the minimum dose required to achieve acceptable analgesia. For patients who experience end-of-dosing failure, an 8-hourly schedule may be employed.

MCR tablets should be swallowed whole and not chewed, crushed, dissolved or broken. Taking broken, chewed or crushed tablets could lead to the release of a toxic dose of morphine.

The MCR formulation is designed to embody release characteristics appropriate to a 12-hour dosing interval. In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours, because the administration of inappropriately-large single doses may lead to acute overdosage.

It is recommended that patients receiving MCR be supplied with a concurrent prescription for immediate-release morphine, which is then readily available to the patient if breakthrough pain is experienced.

Initial Dose and Titration

In opioid-naive patients, for ease of titration, it is recommended that the initial daily dosage of morphine be established using morphine immediate-release tablets (MIR) using a 4-hourly schedule. The total daily dose should then be divided into two and administered as MCR tablets 12-hourly.

Because of the difficulty of titrating MCR, opioid-naive patients who are started directly on MCR therapy should initially receive a conservative dose of 10-20 mg, 12-hourly, in order to avoid overdosage. The majority of patients will then require an upward titration.

Most patients are controlled on 30-100 mg of MCR 12-hourly. However, smaller doses such as 10 mg 12-hourly may be adequate in some patients, while higher doses may be needed in others. As there is no upper limit to the amount of morphine that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia.

During the course of treatment the patient may experience breakthrough pain due to an increase in the level of pain or the development of tolerance to the drug. If this breakthrough pain occurs often, an increase in the dosage may be required. If other measures to relieve pain (e.g., nerve blocks) are employed, the morphine dosage should be reduced to an appropriate level.

Conversion from other Opioid Analgesics

Patients who have previously received other opioids to control their pain may be started directly on MCR therapy using the conversion table below:

	Oral	Parenteral
morphine	1	3
methadone	1.5	3
pethidine	0.1	0.4
pentazocine	0.17	0.5
codeine	0.15	
oxycodone	1	
buprenorphine	35	
nalbuphine		3

1 Calculate the total daily dosage of each opioid (mg)

2 Multiply by the conversion factor shown (this gives the daily total in oral morphine equivalents)

3 Divide by two and administer MCR tablets 12-hourly

4 If the patient is receiving more than one opioid, the morphine equivalents of each opioid should be summed to give the total daily dosage of morphine.

The conversion table is only meant to serve as a guide. In all circumstances, the patient's response following conversion from other opioids must be carefully monitored and the dosage of MCR adjusted accordingly. To reduce the dangers of overdosage the conversion factors have been estimated conservatively for use in one direction - from other opioids to MCR. For this reason the table should not be used where the intention is to convert from MCR to other drugs. The conservative nature of the factors presented means that it is likely that further upward titration may be necessary.

Conversion between MCR and MIR

When converting between these forms, the total daily dosage of morphine should remain the same.

Therefore, when changing from MCR to MIR, the total daily dosage of MCR should be divided into 6 daily doses of MIR.
When changing from MIR to MCR, the total daily dosage of MIR should be divided into two and administered as MCR 12-hourly.

Conversion from Parenteral Morphine to MCR
A 1:3 ratio of parenteral to oral morphine equivalence is suggested. This ratio is conservative and may underestimate the amount of morphine required. If this is the case, the dose of MCR can be gradually increased to achieve acceptable analgesia.

Children:
For children with severe cancer pain, a starting dose in the range of 0.2 to 0.8 mg morphine per kg body weight 12 hourly is recommended. Doses should then be titrated as for adults. Since the controlled release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed, only children who are able to swallow the tables in whole, can use MCR tables.

Post-operative pain:
MCR tablets are not recommended in the first 24 hours post-operatively or until normal bowel function has returned; thereafter it is suggested that the following dosage schedule be observed at the physician's discretion:

1. MCR 10 tablets (1-2 tablets) 12 hourly to patients under 70 kg.
2. MCR 30 tablets 12 hourly to patients over 70 kg.
3. Elderly - a reduction in dosage may be advisable in the elderly.
4. Children - not recommended.

Supplemental parenteral morphine may be given if required but with careful attention to the total dosages of morphine, and bearing in mind the prolonged effects of morphine in this controlled release formulation.

4.3 Contraindications

MCR tablets are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the constituents 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 monoamine oxidase inhibitors or within two weeks of discontinuation of their use

Children under three year of age (see also section 4.2).

Not recommended for pre-operative use or for the first 24 hours post-operatively.

4.4 Special warnings and precautions for use

MCR tablets should be administered with caution in patients with:

- impaired respiratory function
- respiratory depression (see below)
- severe cor pulmonale
- sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence[addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Acute alcoholism
- Delirium tremens
- 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.

Should paralytic ileus be suspected or occur during use, MCR tablets should be discontinued immediately.

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

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

Opioids may 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 manner in some patients. 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.

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

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive MCR tablets for 24 hours prior to the intervention. If further treatment with MCR tablets is then indicated, the dosage should be adjusted to the new post-operative requirement.

MCR tablets should be used with caution post-operatively, and following abdominal surgery as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

It is not possible to ensure bio-equivalence between different brands of prolonged release morphine products. Therefore, it should be emphasised that patients, once titrated to an effective dose, should not be changed from MCR preparations to other slow, sustained or prolonged release morphine or other potent narcotic analgesic preparations without retitration and clinical assessment.

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.

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.

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

Some changes that can be seen with long-term use of opioid analgesics include an increase in serum prolactin, and decreases in plasma cortisol and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Some premenopausal women may have low oestrogen 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).

The controlled release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed. The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine (see section 4.9).

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

Concomitant use of alcohol and MCR tablets may increase the undesirable effects of MCR tablets; concomitant use should be avoided.

Excipients with known effect:

MCR 10 and MCR 30 tablets contain Lactose.
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

MCR 30 tablets contain sunset yellow (E110) which may cause allergic reactions.

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).

Drugs which depress the CNS 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), antidepressants, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol.

Morphine sulfate should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Alcohol may enhance the pharmacodynamic effects of MCR tablets; concomitant use should be avoided.

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

Cimetidine inhibits the metabolism of morphine sulfate.

Plasma concentrations of morphine sulfate 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 sulfate, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine sulfate, and may possibly decrease plasma concentrations of morphine sulfate.

4.6 Fertility, pregnancy and lactation

Pregnancy

MCR tablets are not recommended during pregnancy and labour. 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.

Breast feeding

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

Morphine may modify the patient's reactions to a varying extent depending on the dosage and susceptibility. If affected, patients should not drive or operate 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

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with MCR 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) Sleep apnoea syndrome
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
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Dry mouth Vomiting	Dyspepsia Ileus Taste perversion	
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis
Skin and subcutaneous tissue disorders		Rash	Urticaria	
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenia Fatigue Malaise Pruritus	Peripheral oedema Drug withdrawal syndrome	Drug tolerance Drug withdrawal (abstinence) syndrome neonatal

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 section 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 accordin go the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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.

Crushing and taking the contents of a prolonged release dosage form may lead to the release of morphine in an immediate fashion; this might result in a fatal 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.

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, 1 g/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. MCR tablets will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdose should be modified accordingly.

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 centres.

Morphine depresses the cough reflex by direct effect on the cough centre 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 haemorrhagic or ischaemic 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).

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 MCR tablets and, in general, peak plasma concentrations are achieved 1-5 hours following administration. The availability is complete when compared to an equivalent dose of immediate release oral solution. Morphine is subject to a significant first-pass effect which results in a lower bioavailability when compared to an equivalent intravenous dose.

The major metabolic transformation of morphine is glucuronidation to morphine 3-glucuronide and morphine-6- glucuronide which then undergo renal excretion. These metabolites are excreted in bile and may be subject to hydrolysis and subsequent re-absorption.

Patients are titrated to appropriate pain control using the wide range of strengths of MCR tablets. Consequently, there is a large inter-patient variation in required dosage, the minimum dosage being 5 mg twelve hourly and a dose of 5.6 g 12 hourly has been recorded.

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

Hydroxyethylcellulose, cetostearyl alcohol, magnesium stearate, talc, titanium dioxide(E171).

In addition the tablets contain the following:

MCR 10 contains: Lactose (90 mg), iron oxide E172 (red, yellow and black), polyvinyl alcohol, macrogol/PEG.

MCR 30 contains: Lactose (70 mg), indigo carmine (E132), erythrosine (E127), sunset yellow (E110), hypromellose, polyethylene glycol 400.

MCR 100 contains: Iron oxide E172 (yellow and black), indigo carmine (E132), hypromellose, polyethylene glycol 400.

6.2 Incompatibilities

None stated.

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.

6.5 Nature and contents of container

MCR 10: Blister packs. Pack size: 50 controlled-release tablets

MCR 30: Blister packs. Pack size: 50 controlled-release tablets

MCR 100: Blister packs. Pack size: 20 controlled-release tablets

6.6 Special precautions for disposal and other handling

No special requirements

7. Registration holder

Rafa laboratories Ltd. P.O.Box 405, Jerusalem 9100301

Registration Numbers:

MCR 10: 0664722515

MCR 30: 0580122516

MCR 100: 0316525386

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