SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MXL 150 mg prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Morphine Sulfate 150 mg.

Excipient with known effect:
Each 150 mg prolonged-release capsule contains 0.012 mg of sodium (sodium dodecyl sulfate)

For the full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Capsules, prolonged release

Size 1, blue, hard gelatin capsules containing white to off white multiparticulates and marked MS OD150.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

The prolonged relief of severe and intractable pain.

4.2 Posology and method of administration

Posology
MXL prolonged-release capsules should be used at 24-hourly intervals. The dosage is dependent upon the severity of the pain, the patient's age and previous history of analgesic requirements.

Adults and elderly

Patients presenting with severe uncontrolled pain, who are not currently receiving opioids, should have their dose requirements calculated through the use of immediate release morphine, where possible, before conversion to ***MXL*** prolonged-release capsules.

Patients presenting in pain, who are currently receiving weaker opioids should be started on:

a) 60 mg ***MXL*** prolonged-release capsules once-daily if they weigh over 70 kg.
b) 30 mg ***MXL*** prolonged-release capsules once-daily if they weigh under 70 kg, are frail or elderly.

Increasing severity of pain will require an increased dosage of ***MXL*** prolonged-release capsules using 30 mg, 60 mg, 90 mg, 120 mg, 150 mg or 200 mg alone or in combination to achieve pain relief. Higher doses should be made, where appropriate in 30% - 50% increments as required. The correct dosage for any individual patient is that which controls the pain with no or tolerable side effects for a full 24 hours.

Patients receiving ***MXL*** prolonged-release capsules 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.

Children aged 1 year and above

The use of ***MXL*** prolonged-release capsules in children has not been extensively evaluated. For severe and intractable pain in cancer a starting dose in the range of 0.4 to 1.6 mg morphine per kg bodyweight daily is recommended. Doses should be titrated in the normal way as for adults.

Method of administration

Route of administration: oral

The capsules may be swallowed whole or opened and the contents sprinkled on to soft cold food. The capsule and contents should not be crushed or chewed. ***MXL*** prolonged-release capsules should be used at 24h-hourly interval. The dosage is dependent upon the severity of the pain, the patient's age and previous history of analgesic requirements.

Treatment goals and discontinuation

Before initiating treatment with ***MXL*** prolonged-release capsules, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for

continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with ***MXL*** prolonged-release capsules, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
MXL prolonged-release capsules should not be used longer than necessary.

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

MXL prolonged-release capsules 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 monoamine oxidase inhibitors (MAOIs) or within two weeks of discontinuation of their use.

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

Children under one year of age.

4.4 Special warnings and precautions for use

MXL prolonged-release capsules 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)
- Opioid Use Disorder

- 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.
MXL prolonged-release capsules should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, MXL prolonged-release capsules should be discontinued immediately.

Respiratory depression
The primary 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 preexisting 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of morphine and sedative medicines such as benzodiazepine 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 MXL prolonged-release capsules 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 environment to be aware of these symptoms (see section 4.5).

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as ***MXL*** prolonged-release capsules.

Repeated use of ***MXL*** prolonged-release capsules 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 ***MXL*** prolonged-release capsules 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 (eg. major depression, anxiety and personality disorders).

Before initiating treatment with ***MXL*** prolonged-release capsules 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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. The risk increases with the time the drug is used, and with higher doses. When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse
There is potential for development of psychological dependence [addiction] to opioid analgesics, including morphine. Morphine has an abuse profile similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol and drug abuse. Morphine may be sought and abused by people with latent or manifest addiction disorders.

Parenteral abuse of dosage forms not approved for parenteral administration can be expected to result in serious adverse events, which may be fatal.

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.

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

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.

As with all morphine preparations, patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive MXL prolonged-release capsules for 24 hours prior to surgery. If further treatment with MXL prolonged release capsules is then indicated the dosage should be adjusted to the new postoperative requirement.

MXL prolonged-release capsules should 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.

Prolonged release opioids should not be used for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

MXL prolonged release capsules are not recommended preoperatively or within the first 24 hours postoperatively.

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).

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 MXL prolonged-release capsules to other slow, sustained or prolonged release morphine or other potent narcotic analgesic preparations without retitration and clinical assessment.

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

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.

The prolonged release capsules or their contents (granules) must be swallowed whole, and not broken, chewed, dissolved or crushed. The administration of broken, chewed or crushed morphine granules leads to a rapid release and absorption of a potentially fatal dose of morphine (see section 4.9).

Concomitant use of alcohol and MXL prolonged-release capsules may increase the undesirable effects of MXL prolonged-release capsules; concomitant use should be avoided.

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

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, centrally acting anti-emetics, muscle relaxants, antihypertensives 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.

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

In a study involving healthy volunteers (N = 12), when a 60-mg prolonged - release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule, mean gabapentin AUC increased 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.

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.

Alcohol may enhance the pharmacodynamic effects of MXL prolonged-release capsules; concomitant use should be avoided.

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.

Cimetidine inhibits the metabolism of morphine.

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

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
There are no or limited amount of data from the use of morphine in pregnant women. MXL prolonged-release capsules are not recommended for use in pregnancy and labour due to the risk of neonatal respiratory depression. 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
Administration to nursing mothers is not recommended as morphine is excreted in breast milk.

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

4.7 Effects on ability to drive and use machines

MXL prolonged-release capsules may modify the patient's reactions to a varying extent depending on the dosage and individual 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. 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 you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - The medicine has been prescribed to treat a medical or dental problem; and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law.

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 MXL prolonged-release capsules but should they occur the capsules 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 (see section 4.4) 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
	Very Common	Common	Uncommon	Not known
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction

General disorders and administration site conditions		Asthenia Fatigue Malaise Pruritus	Peripheral oedema	Drug tolerance Drug withdrawal (abstinence) syndrome Drug withdrawal (abstinence) syndrome neonatal

The effects of morphine have led to its abuse and dependence may develop with regular, inappropriate use. This is not a major concern in the treatment of patients with severe pain.

Drug dependence and withdrawal (abstinence) syndrome
Repeated use of ***MXL*** prolonged-release capsules 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).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs of morphine toxicity and overdose are drowsiness, pin-point pupils, skeletal muscle flaccidity, bradycardia, hypotension, pneumonia aspiration, respiratory depression, 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 leads to the release of the morphine in an immediate fashion; this might result in a fatal 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 (50 g 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. ***MXL*** prolonged-release capsules will continue to release and add to the morphine load for up to 24 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 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 Pharmacologic 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 the capsules and, in general, peak plasma concentrations are achieved 2-6 hours following administration. The availability is complete when compared to an immediate release oral solution or MST CONTINUS tablets. The pharmacokinetics of morphine are linear across a very wide dose range. Morphine is subject to a significant first-pass effect which results in a lower bioavailability when compared to an equivalent intravenous or intramuscular 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 reabsorption.

Because of the high inter-patient variation in morphine pharmacokinetics, and in analgesic requirements, the daily dosage in individual patients must be titrated to achieve appropriate pain control. Daily doses of up to 11.2 g have been recorded from twelve-hourly MST CONTINUS tablets. For this reason the capsules have been formulated in strengths of 30 mg, 60 mg, 90 mg, 120 mg, 150 mg and 200 mg.

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

Hydrogenated Vegetable Oil BP
Macrogol 6000 Ph Eur
Talc Ph Eur
Magnesium Stearate Ph Eur

<u>Capsule shells</u>
Gelatin (containing sodium dodecylsulfate)
The following colours are also present:
Erythrosine (E127); indigo carmine (E132); titanium dioxide (E171); iron oxide (E172)

Printing ink
Shellac
Iron oxide, black (E172)
Propylene glycol

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 Years

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

Polypropylene containers with polyethylene caps, containing 28 or 30 capsules.

PVdC (≥ 40 gsm) coated PVC (250 μm) blister strip with aluminium backing foil. The blister strips will be enclosed in a cardboard box. Each box will contain 28 or 30 capsules.

6.6. Instruction for Use/Handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Ltd
Cambridge Science Park
Milton Road

Cambridge CB4 0GW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 16950/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/03/2006

10 DATE OF REVISION OF THE TEXT

22/04/2025