

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Arrow – Morphine LA, 10 mg, 30 mg, 60 mg and 100 mg long acting tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each controlled release tablet contains 10 mg, 30 mg, 60 mg or 100 mg of morphine sulphate.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each 10 mg controlled release tablet is a smooth biconvex buff coloured film coated round tablet embossed with 10 on one side and contains 10 mg Morphine Sulphate Ph.Eur.

Each 30 mg controlled release tablet is a smooth biconvex violet coloured film coated round tablet embossed with 30 on one side and contains 30 mg Morphine Sulphate Ph.Eur.

Each 60 mg controlled release tablet is a smooth biconvex orange coloured film coated round tablet embossed with 60 on one side and contains 60 mg Morphine Sulphate Ph.Eur.

Each 100 mg controlled release tablet is a smooth biconvex grey coloured film coated round tablet embossed with 100 on one side and contains 100 mg Morphine Sulphate Ph.Eur.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arrow – Morphine LA tablets are indicated for the prolonged relief of opioid responsive severe and intractable pain in adults.

Use in Non-Malignant Pain

The use of Arrow – Morphine LA tablets for the treatment of pain which is not due to malignancy should be restricted to situations where:

- All other conservative methods of analgesia have been tried and have failed;
- The pain is having a significant impact on the patient's quality of life;
- There is no psychological contraindication, drug seeking behaviour or history of drug misuse

4.2 Dose and method of administration

Dose

Adults

The dosage is dependent upon the severity of the pain and the patients previous history of analgesic requirements. The tablets should normally be administered twice daily at 12 hourly intervals. One or two 10 mg tablets twice daily is the recommended starting dosage for a patient presenting with severe pain. With increasing severity of pain it is recommended that the dosage of morphine be increased to achieve the desired relief. The dosage may be varied by choosing combinations of available strengths (10 mg, 30 mg, 60 mg and 100 mg) or by using higher strength tablets alone.

It is recommended that a patient transferred from another oral morphine preparation, having a similar bioavailability to immediate release morphine tablets, should receive the same total morphine dose in one 24 hour period. This total dose should be divided between the morning and evening administration. Dosage titration and clinical assessment may be appropriate.

Where a patient had previously received parenteral morphine prior to being transferred to Arrow – Morphine LA tablets, a higher total dosage of morphine may be required. Individual dosage adjustment will be necessary to compensate for any reduction in analgesic effect associated with oral administration.

When Arrow-Morphine LA tablets are to be given for the relief of post operative pain, it is not advisable to administer it during the first 24 hours. Following this initial period, the dosage should be at the physician's discretion.

Some patients may require supplemental parenteral morphine which is perfectly acceptable. Careful attention should be paid to the total morphine dosage however, and the prolonged effects of morphine in the Arrow – Morphine LA tablets should also be borne in mind.

Arrow – Morphine LA tablets should be used with caution post operatively (as with all morphine preparations) but especially in cases of "acute abdomen" and following abdominal surgery. Gastric motility should have returned and be maintained before Arrow – Morphine LA is initiated.

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. Reduced dosing is necessary in patients with renal or hepatic dysfunction, and also in the elderly due to increased sensitivity to its effect.

Paediatric populations

Arrow – Morphine LA tablets are not recommended for paediatric use.

Method of administration

Arrow – Morphine LA tablets should be swallowed whole and not chewed.

4.3 Contraindications

Arrow – Morphine LA tablets are contraindicated in patients

- with respiratory depression especially in the presence of cyanosis and excessive bronchial secretion
- with obstructive airways disease
- with known morphine sensitivity
- with acute hepatic disease
- with acute alcoholism
- with head injuries
- in whom intracranial pressure is raised
- experiencing an attack of bronchial asthma
- for use as a pre-operative medication
- with pheochromocytoma, as morphine appears to increase catecholamine levels
- under 1 (one) year of age
- with chronic pain not due to malignancy who have a prior history of substance abuse
- who are taking or have taken monoamine oxidase inhibitors (MAOIs) within the previous fourteen days.
- with biliary colic
- with heart failure secondary to chronic lung disease
- with paralytic ileus, acute abdomen, or delayed gastric emptying

4.4 Special warnings and precautions for use

Prior to long term prescription, a trial of Arrow – Morphine LA tablets or shorter acting opioids should be undertaken (e.g. for a period of four to six weeks). Long term administration of Arrow – Morphine LA tablets should only occur if this trial demonstrates that the pain is opioid sensitive.

Opioid naïve patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long term therapy.

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.

A single doctor should be responsible for the prescription and monitoring of the patient's opioid use in accordance with guidelines approved by the New Zealand Medical Association.

Special Risk Patients

Arrow – Morphine LA tablets should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, impaired kidney or liver function, prostatic hypertrophy or shock. It should be used with caution in patients with either obstructive bowel disorders or myasthenia gravis.

Drug Dependence and Tolerance: As with other narcotics, tolerance and physical dependence to morphine may develop upon repeated administration and there is potential for abuse of the drug and for development of strong psychological dependence. However, drug abuse is not a problem in patients with severe pain in which morphine is appropriately indicated. Patients on prolonged morphine therapy for pain relief should be withdrawn gradually from the drug if it is no longer required.

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

Use with Other CNS Depressants: Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Arrow – Morphine LA tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Section 4.5 Interactions with other medicines and other forms of interaction].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Arrow – Morphine LA tablets is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Section 4.5 Interactions with other medicines and other forms of interaction].

Impaired Respiration: The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure.

Hypotensive Effect: The administration of morphine may result in severe hypotension in the post-operative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, shock, or the administration of such drugs as the phenothiazines or certain anaesthetics. Morphine may produce orthostatic hypotension in ambulatory patients.

Supraventricular Tachycardias: Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

Acute Abdominal Condition: The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine should be used with caution in patients with inflammatory or obstructive bowel disorders, or with ulcerative colitis, and should only be used when necessary in patients with acute pancreatitis.

Renal or Hepatic Disease: Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may be prolonged.

Caution should be observed when morphine is administered to patients with impaired renal function, as the pharmacologically active metabolite, morphine-6-glucuronide, may accumulate in these patients. This may lead to CNS and respiratory depression.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD): Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency: Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include eg. 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.

4.5 Interaction with other medicines and other forms of interaction

Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalisating agents decrease clearance and so potentiate the effects of morphine.

CNS Depressants: Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants (including benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol)

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma and death.

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 closely for signs of respiratory depression and sedation (see Section 4.4 Special warnings and precautions for use).

Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion.

Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of morphine.

Diazepam, when used following high doses of morphine, exacerbates the hypotensive effects produced by morphine, and is associated with reduced plasma catecholamine levels.

Antihypertensive Agents: Concurrent administration of morphine may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

Muscle Relaxants: Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Mixed Agonist/Antagonist Opioid Analgesics: From a theoretical perspective, mixed agonist/antagonist opioid analgesics (e.g. pentazocine and buprenorphine) should **NOT** be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate the withdrawal symptoms.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion, and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an interaction between the new selective MAOIs (e.g. moclobemide and selegiline) and morphine. Therefore, caution is advised with such drug combinations.

Cimetidine and Other H₂ Receptor Antagonists: There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine. A potentially lethal interaction between cimetidine and morphine, in which the patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported.

Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours. Confusion has also been associated with concomitant use of ranitidine and morphine.

Diuretics: Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

Phenothiazines: The analgesic effect of morphine is potentiated by chlorpromazine.

Amphetamines: Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.

Anticoagulants: Morphine may potentiate the anticoagulant activity of coumarin anticoagulant agents.

Metoclopramide: Morphine may antagonise the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of morphine on gastric emptying.

Zidovudine: Morphine may alter the metabolism of zidovudine, by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Zidovudine and morphine should therefore not be administered concurrently, because the toxicity of either or both of these drugs may be increased.

Ritonavir: Ritonavir may increase the activity of glucuronyl transferases and co-administration with morphine may result in decreased morphine serum level and possible loss of analgesic activity.

Oral Drugs: Morphine delays gastric emptying, so may affect the absorption of orally administered drugs. For example, morphine delays the absorption of paracetamol and mexiletine.

Anticholinergic Agents: Concurrent administration of morphine and anticholinergic agents or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

Antidiarrhoeal Agents: Concurrent administration of morphine and antidiarrhoeal agents with antiperistaltic actions may increase the risk of severe constipation and CNS depression.

Opioid Antagonists: Naloxone antagonises the analgesic, CNS and respiratory depressive effects of morphine, and may precipitate withdrawal in patients who are physically dependent on opioids. Naltrexone blocks the therapeutic effects of opioids, so should be discontinued several days prior to elective surgery if administration prior to, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.

Effect on Laboratory Tests

Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies. Morphine may interfere with hepatobiliary imaging using technetium Tc99m diosfenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of Tc99m diosfenin to the small bowel. These actions result in delayed visualisation, and thus resemble obstruction of the common bile duct.

4.6 Fertility, pregnancy and lactation

Impairment of fertility

Prolonged use of opioids may result in impairment of reproductive function including fertility and sexual dysfunction in both sexes and irregular menses in women.

Use in pregnancy

Category C

Morphine has been associated with foetal CNS defects in rodent studies. It is not known whether morphine can cause foetal harm in humans when administered during pregnancy. Pregnant patients should only be given morphine when the benefits clearly outweigh the risk to the foetus.

Narcotic analgesics may cause respiratory depression and dependence in the newborn infant.

Arrow – Morphine LA tablets are not recommended for use in pregnancy.

Use in lactation

Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving morphine. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine is stopped.

4.7 Effects on ability to drive and use machines

Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Morphine in combination with other opioid analgesics, phenothiazines, sedative-hypnotics and alcohol have additive depressant effects. Patients should be cautioned accordingly.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Uncommon Hypersensitivity
Very rare Anaphylactic reaction, anaphylactoid reaction

Gastrointestinal

Common Anorexia, dyspepsia, vomiting
Uncommon Biliary pain, gastrointestinal disorders, ileus, taste perversion
Very rare Abdominal pain
Not known Nausea, constipation, dry mouth

Nervous system disorders

Uncommon Headache
Rare Intracranial pressure increased
Not known Sedation, somnolence, allodynia, hyperalgesia, hyperhidrosis

Psychiatric disorders

Uncommon Agitation, mood altered, hallucinations, disorientation
Rare Insomnia
Not known Dependence

Eye disorders

Very rare Vision blurred
Not known Miosis

Ear and labyrinth disorders

Uncommon Vertigo

Genitourinary

Uncommon Amenorrhea, decreased libido, erectile dysfunction, hypogonadism

Cardiovascular

Uncommon Hypotension, syncope
Rare Bradycardia and tachycardia
Not known Palpitations

Hepatobiliary

Rare Biliary colic, increased hepatic enzymes
Not known Exacerbation of pancreatitis

Renal and urinary disorders

Uncommon Urinary retention

Investigations

Rare Blood pressure decreased

Respiratory

Common Cough decreased
Rare Bronchospasm
Not known Respiratory depression

Skin and subcutaneous tissue disorders

Common Rash
Uncommon Hyperhidrosis
Rare Urticaria, pruritus

General

Common Sweating
Uncommon Facial flushing, hypertonia, tolerance
Very rare Chills, asthenia
Not known Syncope, drug withdrawal (abstinence) syndrome (eg, dysphoric mood, anxiety)

Withdrawal (Abstinence) Syndrome: Chronic use of opioid analgesics may be associated with the development of physical dependence, with or without psychological dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered.

Withdrawal symptoms that may be observed after discontinuation of opioid use include: body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (<https://nzphvc.otago.ac.nz/reporting/>).

4.9 Overdose

Symptoms

Signs of morphine toxicity and overdose are pin-point pupils, respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. In addition, dropping of body temperature, and relaxation of skeletal muscles were observed.

Pneumonia aspiration. Overdose can result in death.

Death may occur from respiratory failure.

Treatment

Immediate attention should be given to the re-establishment of adequate respiratory exchange through provision of a patient airway and institution of assisted or controlled ventilation. In patients physically dependent on opioids, respiratory support is the first line of treatment. In these patients, the use of naloxone is potentially dangerous. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, The recommended adult dose of naloxone for the treatment of severe opiate induced respiratory depression is 0.4 to 2mg intravenously every 2 to 3 minutes as necessary simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01mg/kg naloxone. A response should be seen after 2 to 3 doses. Note the duration of action of naloxone is usually shorter than that of morphine and thus the patient should be carefully observed for signs of CNS depression returning.

If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage.

Naloxone should be administered cautiously to persons who are known or suspected to be physically dependant on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will

depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Morphine toxicity may be a result of overdose but because of the large inter-individual variation in sensitivity to opioids, it is difficult to assess the exact dose of any opioid that is toxic or lethal. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being observed.

The physician should be aware that Arrow – Morphine LA tablets remaining in the intestine will continue to release morphine sulphate for a period of hours.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids; fibrates, ATC code: N02AA01

Morphine is an opioid analgesic. It acts mainly on the central nervous system and on smooth muscle. Morphine combines selectively at opioid binding sites found in the CNS and smooth muscle to produce its pharmacologic effects. These are due to morphine mimicking the action of endogenous endorphins, which are released in response to pain and other stimuli. Morphine relieves most types of pain but is more effective against dull, constant pain than sharp, intermittent pain. Analgesia at the supraspinal level results principally from combination with μ (mu) receptors. K (kappa) receptors are responsible primarily for expression of analgesia at the spinal level. In addition to relieving severe constant pain, morphine also alleviates the associated anxiety.

Although morphine is predominantly a central nervous system depressant it has some central stimulant actions which results in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially that at the sphincters of the gastro-intestinal tract.

Morphine and related analgesics may produce both physical and psychological dependence and should therefore be used with discrimination. Tolerance may also develop.

Morphine is an analgesic used for the symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction and surgery. When pain is likely to be of short duration, a short-acting analgesic is usually preferred. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain. It is useful as a hypnotic where sleeplessness is due to pain and may also relieve the pain of biliary or renal colic, although an antispasmodic may also be required since morphine may increase smooth muscle tone.

Morphine reduces intestinal motility and is used in the symptomatic treatment of diarrhoea. It also relieves the dyspnoea of left ventricular failure and of pulmonary oedema. It is effective for the suppression of cough, but codeine is usually preferred, as there is less risk of dependence. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures. Morphine is usually administered as the sulphate although the hydrochloride and the tartrate are used in similar doses; the acetate has also been used. Routes of administration include the oral, subcutaneous, intramuscular, intravenous, intraspinal and rectal routes. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

The onset of action of Arrow – Morphine LA tablets is about 30 to 45 minutes after oral administration and, due to its slow release formulation, the duration of action is 12 hours.

5.2 Pharmacokinetic properties

Morphine has a plasma half life of about 2 to 3 hours and if given IV must be administered frequently. Arrow – Morphine LA tablets, being a sustained release preparation of morphine, has the advantage that it is only administered twice daily.

Morphine is well absorbed from the GI tract following administration of Arrow – Morphine LA tablets, however, it is subject to extensive first-pass metabolism in the liver. The elimination half-life of morphine is 2 to 3 hours with great interpatient variability.

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

Morphine is widely distributed through the body and diffuses across the placenta.

A summary of the morphine pharmacokinetic parameters is given below:

- Plasma half life: about 2 to 3 hours
- Volume of distribution: about 3 to 5 litres/kg
- Plasma clearance: about 15 to 20 ml/min/kg
- Protein binding in plasma: 20 to 35 %

Pharmacokinetic parameters pertinent to Arrow – Morphine LA tablets are summarised in the following table:

PARAMETER	ARROW-MORPHINE LA tablets Fasting	ARROW-MORPHINE LA tablets Food
AUC _(0-t) (ng·h/ml)	46.02 ± 18.85	59.88 ± 20.52
C _{max} (ng/ml)	9.2 ± 3.6	13.6 ± 4.6
t _{max} (hours)	2.5 ± 1.7	3.9 ± 1.6

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Hydroxyethylcellulose, Hypromellose, Povidone, Talc and Magnesium Stearate.

Colorants: E171, E172 - 10 mg, E110, E127, E132 - 30 mg, E171, E110 - 60 mg, E171, E172 - 100 mg.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture.

6.5 Nature and contents of container

Blister packs. Pack size of 1, 10, 20, 1000 tablets.

Polypropylene bottle: Pack size of 10 tablets.

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Controlled Drug Class B1

8. SPONSOR

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9. DATE OF FIRST APPROVAL

5 May 1994

10. DATE OF REVISION OF THE TEXT

6 June 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.8, 4.9	Updated safety information in accordance with Teva CCSI No. 21/04/08/18