

DATA SHEET

ARROW – MORPHINE LA

Morphine Sulphate Ph.Eur. 10 mg, 30 mg, 60 mg and 100 mg long acting tablets

Presentation

10 mg tablets

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.

30 mg tablets

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.

60 mg tablets

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.

100 mg tablets

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.

Uses

Actions

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. κ (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 30-45 minutes after oral administration and, due to its slow release formulation, the duration of action is 12 hours.

Pharmacokinetics

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

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 ₍₀₋₄₎ (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

Indications

ARROW-MORPHINE LA tablets are indicated for the prolonged relief of opioid responsive severe and intractable pain.

Dosage and Administration

ARROW-MORPHINE LA tablets should be swallowed whole and not chewed.

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.

ARROW-MORPHINE LA tablets are not recommended for paediatric use.

Contraindications

Respiratory depression especially in the presence of cyanosis and excessive bronchial secretion, obstructive airways disease, known morphine sensitivity or acute hepatic disease. It is also contraindicated in the presence of acute alcoholism, head injuries and conditions in which intracranial pressure is raised. Neither should it be given during an attack of bronchial asthma nor in heart failure secondary to chronic lung disease.

ARROW-MORPHINE LA tablets are contraindicated in patients with paralytic ileus, acute abdomen, or delayed gastric emptying.

ARROW-MORPHINE LA tablets are not to be used as a pre-operative medication.

ARROW-MORPHINE LA tablets should not be used in patients with pheochromocytoma, as morphine appears to increase catecholamine levels.

ARROW-MORPHINE LA tablets are contraindicated in children under 1 (one) year of age.

ARROW-MORPHINE LA tablets are contraindicated in patients with chronic pain not due to malignancy who have a prior history of substance abuse.

Warnings and Precautions

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.

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.

Narcotic analgesics may cause respiratory depression and dependence in the newborn infant. Use in pregnancy and breast-feeding is, therefore, not recommended.

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.

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

A single doctor should be responsible for the prescription and monitoring of the patient's opioid use.

Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. Jones D & Shug S., *Opioids in Chronic Pain of Non-Malignant Origin: An Interim Consensus* NZMJ 108: 492, 24 November 1995).

Use in pregnancy: Category C. **ARROW-MORPHINE LA** tablets are not recommended for use in pregnancy.

Use in lactation: Although morphine has been reported to be secreted in breast milk, clinically important concentrations of the drug are probably not present following usual therapeutic doses.

Effects on ability to drive and use machines: Morphine may impair the mental and/or physical abilities needed for driving a car or operating machinery. Patients should be cautioned accordingly.

Adverse Effects

The adverse effects listed below are classified by body system according to their incidence (common [$\geq 1\%$] or uncommon [$< 1\%$]).

Gastrointestinal

Common

abdominal pain
anorexia
constipation
dry mouth
dyspepsia
nausea
vomiting

Uncommon

biliary pain
gastrointestinal disorders
ileus
taste perversion

Central Nervous System

Common

asthenia
confusion
headache
insomnia
involuntary muscle contractions
somnolence

Uncommon

thought abnormalities
agitation
dysphoria
euphoria
hallucinations
malaise
mood changes
respiratory depression
seizure
paresthesia
vertigo
vision abnormalities
withdrawal syndrome

Genitourinary

Uncommon

amenorrhea
decreased libido
impotence
urinary retention

Cardiovascular*Uncommon*hypotension
syncope**Metabolic and Nutritional***Uncommon*peripheral edema
pulmonary edema**Respiratory***Common*bronchospasm
cough decreased
respiratory depression**Dermatological***Common*

rash

Uncommon

urticaria

General*Common*

chills

pruritus

sweating

Uncommon

allergic reaction

anaphylactic/anaphylactoid reactions

drug dependence

facial flushing

hypertonia

miosis

tolerance

Interactions

ARROW-MORPHINE LA tablets should not be concurrently administered with monoamine oxidase inhibitors (MAOI's) or used within two weeks of discontinuation of MAOI use.

The depressant effects of morphine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants and phenothiazines.

The action of morphine may in turn affect the activities of other compounds; for example its gastrointestinal effects may delay absorption as with mexilitine or may be counteractive as with metoclopramide.

Morphine may competitively inhibit the hepatic glucuronidation of zidovudine thus reducing its clearance. Concurrent use of **ARROW-MORPHINE LA** tablets and zidovudine should be avoided because the toxicity of either or both medicines may be potentiated.

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

Cimetidine inhibits the metabolism of morphine.

Overdosage

Signs of morphine toxicity and overdose are likely to consist of pin-point pupils, respiratory depression and hypotension. Circulatory failure and depending coma may occur in more severe cases.

In acute poisoning by **ARROW-MORPHINE LA** tablets the stomach should be emptied by aspiration and lavage. A laxative may be given to aid peristalsis. Treatment of respiratory failure and shock may require intensive supportive therapy. In addition to this the specific antagonist naloxone hydrochloride should be administered at a dose of 0.4 to 2 mg IV. This dose should be repeated at intervals of 2 to 3 minutes if required, up to a total dose of 10 mg.

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.

Pharmaceutical Precautions

Shelf life: 36 months. Store below 25 °C. Protect from light and moisture. Keep out of reach of children.

Medicine Classification

Controlled Drug B1

Package Quantities

10 mg, 30 mg, 60 mg and 100 mg tablets: bottles or cartons of 10 tablets.

Further Information

Morphine sulphate is the pentahydrate of the sulphate of 7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6-diol. It has a molecular formula and weight of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ and 758.8 respectively.

Other ingredients of the tablets are: 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.

Name and Address

Arrow Pharmaceuticals (NZ) Limited
Mount Eden Central Business Park
33a Normanby Road, Mt. Eden
Auckland, New Zealand

Date of Preparation

16 February 2011