

LAVOISIER MORPHINE (SULFATE) 1 mg/ml, injectable solution

QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulfate of MORPHINE 1.00 mg
in each 1 ml of injectable solution

For excipients, see section on pharmaceutical data

1 ml ampoule contains 1 mg of morphine sulfate

PHARMACEUTICAL FORM

Injectable solution

THERAPEUTIC INDICATIONS

Intense pains and/or not responsive to non-opioid analgesics.

DOSES AND ADMINISTRATION

Note that ONE mg of morphine sulfate is equivalent to ONE mg of morphine hydrochlorate.

Interaction between dose, efficacy and tolerance varies significantly from one patient to another. It is then essential to often evaluate efficacy and tolerance and gradually adjust posology to patient's requirements. No maximal dose, as long as adverse effects can be controlled.

Intramuscular route is not recommended because painful and has no kinetic benefit versus subcutaneous route.

Epidural, intrathecal and intraventricular routes require that:

- morphine be used FREE OF PRESERVATIVE,
- the solution be FILTERED PRIOR TO INJECTION through a filter of 0.22 µm (to prevent any potential specific contamination after initial closure puncture).

Order of equivalence of doses according to routes of administration, as suggested indication:

Oral use	Subcutaneous	Intravenous	Epidural	Intrathecal
1 mg	1/2 to 1/3 mg	1/2 to 1/3 mg	1/10 to 1/20 mg	1/50 to 1/200 mg

Morphine should not be administered concomitantly via two different routes because of the potential for overdosage by kinetic differences between several administration routes.

Method of acute pain management (in particular post-operative):

Intravenous and subcutaneous routes:

In adults, morphine is delivered intravenously most often in a fractional way ('titration'), with a dose from 1 to 3 mg (depending on background, mainly patient's age), approximately every 10 minutes, until satisfactory analgesia is attained (or onset of undesirable effects) and with patient being continuously monitored.

If necessary to switch treatment, it may be either subcutaneous injections from 5 to 10 mg every 4 to 6 hours, or patient controlled analgesia intravenously with bolus from 0.5 to 1 mg followed by a period with no possible injection ('refractory period') of about 10 minutes.

Morphine in intravenous infusion (1 to 5 mg/h) is usually indicated in patients under controlled ventilation in intensive care unit.

In children, morphine is generally delivered intravenously in a fractional way ('titration'). An initial dose from 0.025 to 0.1 mg/kg (depending on background, patient's age mainly) is followed, if need be, of bolus of approximately 0.025 mg/kg every 5 to 10 minutes, until satisfactory analgesia is attained (or onset of undesirable effects) and with patient being continuously monitored.

If to switch treatment is needed, it may be a continuous intravenous infusion from 0.01 to 0.02 mg/kg/h under medical monitoring in recovery room or intensive care unit.

Patient controlled analgesia (PCA) by intravenous injection may be achieved in children from 6 years, with bolus from 0.015 to 0.02 mg/kg followed by a period with no possible injection ('refractory period') for 10 to 15 minutes. It may be associated with a continuous dose of 0.005 to 0.02 mg/kg/hour.

Because painful, subcutaneous route is not recommended for use in children.

Epidural route:

In adults: 2 to 6 mg every 12 to 24 hours.

In children: 0.03 to 0.05 mg/kg, repeat injections if need be, depending on clinical monitoring after 12 to 24 hours.

Intrathecal route:

In adults: 0.1 to 0.2 mg every 12 to 24 hours.

Treatment of chronic pains (especially resulting from malignant disease):

Initial doses are dependent on the administration route

Doses in children are not different from adults on a mg/kg basis.

Subcutaneous route:

In patients with no previous oral morphine treatment, the daily initial posology must be 0.5 mg/kg/day (usually 30 mg/day in adults), preferably in continuous infusion (rather than in intermittent injections every four to six hours).

In patients receiving previous oral morphine use, the daily initial posology must be half of the oral posology administered. In inadequate posology dose, the switch to larger posology can be performed right away (see posology adjustment section).

Intravenous route:

In patients with no previous oral morphine treatment, the daily initial posology must be 0.3 mg/kg/day (usually 20 mg/day in adults), in continued infusion preferably.

In patients receiving previous oral morphine use, the daily initial posology must be one the third of the oral posology administered. In inadequate posology dose, the switch to larger dose can be performed right away (see posology adjustment section).

In patients with pain varying in intensity during the day, a method of patient controlled analgesia (PCA) may be used: continuous infusion (with usual posology) should be associated with self-administered bolus equivalent to approximately one hour of infusion. Each bolus must be followed by a period with no possible injection ('refractory period') of 10 minutes minimum.

- ***Epidural, intrathecal and intraventricular routes:***

In chronic pains, these routes should be used when the other administration methods cause unacceptable adverse reactions.

As suggested posology levels:

- Initial daily posology by epidural route, over 1 or 2 injections, is approximately 1/10th of parenteral posology,
- the initial daily posology by intrathecal route, over 1 or 2 injections, is about 1/100th of parenteral posology,
- Intraventricular route is exceptionally used by some expert clinicians (the initial posology is about 0.1 to 0.2 mg/24h).

Posology adjustment

- ***Evaluation rate*** (based on the extent of pain relief and the presence of adverse effects)
Suspension of treatment if posology adjustment is ineffective. The patient should then be observed very often, essentially at the onset of treatment, as long as the pain is still out of control.
- ***Posology increase***
If the pain is not under control, the daily morphine posology should be increased by approximately 30 to 50 %.
In the process of posology adjustment, there is no maximal posology as long as adverse effects can be controlled.

CONTRA-INDICATIONS

This drug should never be used in patients with:

- hypersensitivity to morphine or to any of the other agents,
- depressed respiratory insufficiency (in the absence of artificial ventilation),
- severe hepato-cellular insufficiency (with encephalopathy),
- in acute: cranial traumatism and intracranial hypertension in the absence of controlled ventilation,
- epilepsy not under control,
- associations with buprenorphine, nalbuphine and pentazocine (see Drug Interactions)
- in breastfeeding mothers, at onset or continuation of a long-term treatment after birth.

Contraindications to epidural, intrathecal and intraventricular routes:

- hemostasis disorders when performing the procedure,
- evolutive local skin infections, regional or systemic,
- evolutive intracranial hypertension.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

In pain management context, increasing the dose is not related to an addictive process in most cases.

An urgent and repeated demand requires that patient's state be often reevaluated. Most often it reflects a genuine need in analgesic, not to be confused with an addictive behavior.

Morphine is an opioid analgesic which may lead, apart from its use in pain management, to an indirect use (misuse): physical and psychic dependence may then be observed, as well as a tolerance (addiction) developing after repeat injections.

However, antecedents of drug-addiction are not contraindication to morphine prescription if absolutely necessary in pain management.

Depending on the duration of treatment, dose administered and progression of pain, morphine suspension should be gradual to prevent withdrawal syndrome. Symptoms of withdrawal syndrome include: anxiety, irritability, shivers, mydriasis, flushing, sudation, watering of the eyes, rhinorrhea, nausea, vomiting, abdominal cramps, diarrhoea, arthralgia.

Use of injectable morphine requires that pain intensity, vigilance and respiratory function be monitored, all the more closely since the pain is acute, the onset of treatment recent and the route of administration central. Drowsiness is a warning signal of respiratory decompression.

Special warnings and precautions for use

Morphine should be used with caution in patients with:

- ***Hypovolemia:***
In case of hypovolemia, morphine may induce a collapse. Hypovolemia will then be corrected prior to administration of morphine.
- ***Renal failure:***
Excretion of morphine through the kidney, in the form of an active metabolite requires that treatment be initiated with reduced posology while adjusting later, dose or frequency to clinical state, as is the case with any other patient.
- ***When etiology of pain is treated concomitantly:***
It is essential then that morphine doses be adjusted to the results of the applied therapy.
- ***In patients with respiratory insufficiency, 'not decompensated':***
Respiratory rate must be closely monitored. Drowsiness is a warning signal of respiratory depression.
It is essential that morphine doses be reduced when other analgesic treatments with central action are prescribed concomitantly, because of the potential for a sudden onset of respiratory insufficiency.
- ***In patients with hepatic insufficiency:***
Morphine should be administered with caution and associated with clinical monitoring.
- ***In older or very old patients :***
Their particular hypersensitivity to analgesic effects but also to adverse effects on the central nervous system (confusion) or gastric, associated with a physiological diminution in renal function must make particularly cautious and reduce to half the initial posology.
A prostatic urethra or vesical pathology, common among this population, exposes to the risk of urinary obstruction.
Coprescriptions of psychotropic treatments, CNS depressant or with anticholinergic effect potentiate the onset of adverse reactions.
- ***Constipation:***
It is essential to ensure that an occlusive syndrome is not present prior to initiating the treatment. Constipation is a known morphine adverse drug reaction. Prescription of a preventive treatment must be systematic.
- ***In neonates, especially under three months:***
Effects of morphine are more potent and prolonged by defect of maturation of their metabolism. The initial doses must be reduced. The treatment of acute pains should be monitored in intensive care unit. Chronic treatment must be initiated under hospital monitoring.

- Intracranial hypertension:

In case of intracranial pressure, the use of morphine in chronic pain should be exercised with caution.

- Micturition disorders:

Dysuria or urine retention may occur primarily by intrathecal and epidural routes.

- Sportsmen :

Sportsmen should be warned that this specialty contains morphine and that this active ingredient is registered on the list of the doping substances.

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS

It should be borne in mind that several drugs or substances may potentiate the depressant effects on the central nervous system and cause a decrease in vigilance. These are derivatives of morphine (analgesics, antitussives and adjuvant treatments), neuroleptics, barbiturates, benzodiazepines, Anxiolytics other than benzodiazepines (for example meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapin, trimipramine), sedatives H1-antihistamines, central antihypertensives, baclofen and thalidomide.

Contraindicated interactions:

◆ **Agonists- antagonists morphinic analgesics (buprenorphine, nalbuphine, pentazocine):**

Decreased analgesic or antitussive effect by concurrent block of receptors, and risk of onset withdrawal syndrome.

Not recommended association:

◆ **Naltrexone**

Analgesic effects may subside.

If needed, doses of morphine derivatives can be increased.

◆ **Alcohol intake:**

Potential of the sedative effects of these substances by alcohol.

Modification of vigilance may impair the ability to drive and use machines.

Alcoholic beverages and alcohol-containing medications must be avoided.

Associations subjected to precautions for use :

◆ **Rifampicin**

Decrease of concentrations and efficacy of morphine including its active metabolite. Clinical monitoring should be achieved and if need be, posology adjustment of morphine during treatment with Rifampicin and after its suspension.

Associations requiring extreme caution:

◆ **Other agonist morphinic analgesics** (alfentanil, codeine, dextromoramide, dextropropoxyphene, dihydrocodeine, fentanyl, oxycodone, pethidine, phenoperidine, remifentanil, sufentanil, tramadol)

◆ **Antitussives containing substituted porphyrin** (dextrometorphan, noscapine, pholcodine)

◆ **Opioid antitussives** (codeine, ethylmorphine)

◆ **Barbiturates**

◆ **Benzodiazepines and related,**

Increased risk of central respiratory depression, potentially life-threatening in case of overdose.

◆ **Other sedative medications**

Potential of central depression. A decrease in vigilance may impair the ability to drive vehicles and operate machinery safely.

PREGNANCY AND LACTATION

Pregnancy

The studies carried out on animals did not show any evidence of a teratogenic effect of morphine.

In clinical trials, no particular malformative effect of morphine has been reported until now. However, only epidemiologic studies would give evidence to the absence of risk.

High doses, even during a treatment over a short period of time, just before or during labour for delivery are likely to induce respiratory depression in neonates. Furthermore, in the last months of pregnancy, mothers receiving chronic treatment of morphine, regardless of the dose, may be conducive to withdrawal syndrome in neonates. In these conditions of use, neonatal monitoring will be considered.

Consequently, providing these precautions are taken, morphine may be prescribed in pregnancy if clearly considered.

Lactation

- A single dose seems to cause no harm to newborns.

- In repeat administration of morphine over a few days, breast-feeding should be suspended momentarily.

- At onset or continuation after birth of a long-term treatment, it is contraindicated in breastfeeding mothers.

Effect on the ability to drive vehicles and use machines

Because of the possible fall in vigilance induced by this drug, attention should be drawn to the dangers of operating a vehicle or machinery, primarily at initiation of treatment and in association with other depressors of the central nervous system.

ADVERSE REACTION

The most commonly reported adverse effects at initiation of treatment include somnolence, confusion, nausea and vomiting. They may be transitory but when persisting a related cause or an overdose must be investigated. However, constipation does not affect the continuation of treatment. All the effects are predictable and require to be treated.

Other effects may also be observed:

- sedation, agitation, nightmares, more particularly in elderly patients, with possible hallucinatory phenomena,

- confusion, sedation, agitation, nightmares, more particularly in elderly patients, with possible hallucinatory phenomena,

- respiratory depression to the point of apnea,

- increase of intracranial pressure should be treated first,

- dysuria and urinary obstruction, primarily in patients with prostatic adenoma or urethral stenosis,

- pruritus and skin irritation (mainly for intrathecal and epidural routes)

- symptoms of withdrawal syndrome by abrupt suspension of treatment include: yawning, anxiety, irritability, insomnia, shivers, mydriasis, flushing, sweating, watering of the eyes, rhinorrhea, nausea, vomiting, anorexia, abdominal cramps, diarrhoea, myalgias, arthralgias.

- In older patients or patients with renal failure, the onset of myoclonias may exceptionally occur in case of overdose or when dosage increase is too fast.

OVERDOSAGE

Symptoms:

Drowsiness is a warning signal of onset of respiratory decompensation.

Acute myosis, hypotension, hypothermia, coma may also be observed.

Emergency procedures:

- Suspension of morphine treatment.
- Stimulation-assisted ventilation, before cardio-respiratory resuscitation in intensive care unit.
- Specific treatment by naloxone: First placement of a route of administration and monitoring of the time required until symptoms subside.

CLINICAL PHARMACOLOGY

Pharmacodynamics

OPIOID ANALGESIC codes ATC N02 AA01 (N: central nervous system)

Action on central nervous system

Morphine has a dose-dependent analgesic action. It may act on psychomotor behavior and cause, depending on the dose and background, either sedation or agitation.

On respiratory centers and that of cough, morphine exerts from the onset of therapeutic doses, a depressive action. The depressor respiratory effects of morphine subside in chronic treatment.

Action of morphine on the vomiting center, (via the chemoreceptor trigger zone (CTZ), particularly through stimulation by pain and cochleo-vestibular space), and on gastric emptying (see below) endows it with variable emetic properties.

Finally morphine results in myosis from central nervous system.

Action on the smooth muscle

Morphine decreases tonicity and peristalsis of longitudinal fibres while increasing tonicity of circular fibres, causing spasm on sphincters (pylorus, ileum-caecal valvula, anal sphincter, Oddi's sphincter, vesical sphincter).

Pharmacokinetics

Resorption

- Since it is more quickly resorbed in blood by epidural route (via large venous plexus) than by intrathecal (via small medullary capillaries), morphine-induced analgesia has a sustained-release action by intrathecal route.
- By epidural and intrathecal route, supraspinal distribution is delayed.
- Biodisponibility of oral administration compared to those administered by subcutaneous route is 50 %.
- Biodisponibility of oral administration compared to that administered by intravenous route accounts for 30 %.

Distribution

After resorption, the binding of morphine to plasma proteins accounts for 30 %. Morphine crosses the hematoencephalic barrier and placenta.

Metabolism

Morphine is highly metabolized in glucuronoconjugated derivatives which go through an entero-hepatic cycle.

6 -glucuronide and normorphine are two active metabolites of the substance-mother.

Elimination:

- Plasma half-life of morphine varies (from 2 to 6 hours).
- Elimination of glucuronoconjugated derivatives is primarily through urine, both by glomerular filtration and tubular secretion. Elimination in the feces is low (<10 %).

PHARMACEUTICAL DATA

List of excipients

Sodium chloride, hydrochloric acid, water for injectable preparations

Incompatibilities

Acid solutions. Iodine solutions.

Admixtures with other injectable solutions are not recommended for use unless validated by qualified team.

Shelf life

3 years

Storage special precautions

To be stored in outer packaging, in a dark place.

Nature and contents of container

1 ml ampoule bottle (type I glass)

Directions for use, handling and discarding

To be used immediately after initial closure puncture. Discard unused portions of the liquid.

HOLDER OF MARKETING APPROVAL

CDM LAVOISIER - LABORATOIRES CHAIX ET DU MARAIS – 7, RUE LABIE - 75017 PARIS

PACKAGING AND PRODUCT LICENSE NUMBER

MORPHINE SULFATE 1 mg/ml, injectable solution - ampoule (glass)

MA 356 206-9: 1 ml - 10 units pack - Reimbursed by French Health Care Security 65% - Public Price including VAT: 9,00 € - Approved for institutions

DATE OF THE FIRST MARKETING APPROVAL

March 2001

DATE OF REVISION

December 2006

HOW SUPPLIED

Opioid: prescription limited to 7 days, or 28 days with perfusion using computerized systems. Available on prescription meeting the requirements ordained by decree of 31 March 1999.

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