SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Actimorph 20 mg Orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 20 mg of morphine sulfate corresponding to 15.04 mg of morphine.

Excipient(s) with known effect
Each 20 mg orodispersible tablet contains:
Benzyl alcohol (0.8 microgram/orodispersible tablet)
Sulphites (28.0 nanogram/orodispersible tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Actimorph 20 mg Orodispersible tablets are round, convex, 11 mm of diameter, white tablets engraved “20” on one side and smooth on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain which can be adequately managed only with opioids.

4.2 Posology and method of administration

Treatment goals and discontinuation
Before initiating treatment with Actimorph, a treatment strategy including treatment duration and treatment goals, and a plan for end of 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 Actimorph, 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).

Posology

Actimorph Orodispersible tablets should be administered as follows:

Population	***Starting dose***
Adults and adolescents over 16 years	10-20 mg of morphine sulfate every 4-6 hours

The dose should then be carefully titrated, every day if necessary, to achieve pain relief.
Patients already receiving opioids may be initiated on higher doses depending on their previous opioid experience.

If used for dose titration Actimorph Orodispersible tablets should be taken in a fixed time schedule (every 4 to 6 hours).

The correct dose for any individual patient is that which will maintain adequate analgesia with acceptable undesirable effects.
The dose can be increased under medical supervision according to the intensity of the pain the sensitivity and the previous history of analgesic requirements of the individual patient.

Duration of treatment

This medicinal product should not be used longer than necessary.
If the need for long-term pain treatment is anticipated in view of the nature and severity of the illness, the patient should be switched to prolonged-release analgesics. The total daily dose should be the same.

If used as breakthrough pain medication, the need for more than two occasions per day is usually an indication that the prolonged-release dose requires upward titration.

Actimorph Orodispersible tablets can be taken with or without food.

Correspondence between the different routes of administration

The posology of morphine varies depending on the route of administration. Switching from a morphine pharmaceutical form to another must take conversion factors into account in order to maintain the same amount of morphine available.
The dose should be divided by 3 when patients are transferred from an oral morphine form to an intravenous form, and halved when transferred to a subcutaneous form.

Special populations

Elderly

A reduction in dose may be advisable in the elderly (dose reduction such as 2.5-5 mg every 4-6 hours).

Patients with hepatic or renal impairment

In patients with hepatic or renal impairment, Actimorph Orodispersible tablets should be administered with particular care.

Patients with suspected delayed gastrointestinal passage
In patients with suspected delayed gastrointestinal passage, Actimorph Orodispersible tablets should be administered with particular care.

Paediatric population

Population	***Starting dose***
Adolescents 13-16 years (40-60 kg)	5-20 mg of morphine sulfate (corresponding to about 0.1 to 0.5 mg/kg) every 4-6 hours
Children 6-12 years (18-40 kg)	5-10 mg of morphine sulfate (corresponding to about 0.1 to 0.5 mg/kg) every 4-6 hours
Children 1-5 years (9-18 kg)	2.5-5 mg of morphine sulfate (corresponding to about 0.1 to 0.5 mg/kg) every 4-6 hours
Children > 6 months (6-9 kg)	1 mg of morphine sulfate (corresponding to about 0.1 to 0.2 mg/kg) every 4-6 hours

Actimorph Orodispersible tablets are contraindicated in children under 6 months of age (see section 4.3).

Method of administration
Actimorph Orodispersible tablets are for oral use. The tablet disperses rapidly in the mouth and is then swallowed.
Alternatively, for special population such as children or patients with difficulties in swallowing, the tablet may be placed in a spoon with the addition of a small quantity of water until sufficient dispersion to allow ingestion. This method of administration should be used in children below the age of 6 years.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- Children under 6 months old,
- Severe respiratory depression with hypoxia and/or hypercapnia (in absence of artificial ventilation),
- Severe bronchial asthma,
- Severe chronic obstructive pulmonary disease,
- In acute: cranial trauma and intracranial hypertension in absence of controlled ventilation,
- Uncontrolled epilepsy,
- Acute hepatic disease,
- Acute abdomen,
- Paralytic ileus,
- Delayed gastric emptying,

- Concomitant administration with opioid agonists-antagonists (e.g. buprenorphine, nalbuphine, pentazocine), opioid partial agonists (e.g. naltrexone, nalmefene), sodium oxybate,
- Concurrent administration of mono-amine oxidase inhibitors or within two weeks of discontinuation of their use.

4.4 Special warnings and precautions for use

A particularly careful medical supervision and if necessary dose reduction is recommended in the following cases:

- Dependence on opioids, patients with a history of substance abuse,
- Impaired respiratory function,
- Respiratory depression (see below),
- Sleep apnoea,
- Cor pulmonale,
- Head injury, intracranial lesions or conditions with increased intracranial pressure, if ventilation is not performed,
- Impaired consciousness,
- Hypotension with hypovolemia,
- Prostatic hyperplasia with residual urine formation (risk of bladder rupture due to urinary retention),
- Urinary tract narrowing or colic of the urinary tract,
- Biliary tract disorders,
- Obstructive and inflammatory bowel disease,
- Constipation,
- Pheochromocytoma,
- Adrenocortical insufficiency,
- Pancreatitis,
- Severely impaired renal function,
- Severely impaired hepatic function,
- Hypothyroidism,
- Epileptic seizure disorders or increased susceptibility to seizures,
- Elderly patients.

Respiratory depression

The major risk of opioid overdose 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 increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of Actimorph Orodispersible tablets and sedative medicinal products, such as benzodiazepines or related medicinal products, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be

reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Actimorph Orodispersible tablets concomitantly with sedative medicinal products, the lowest effective dose should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Morphine has an abuse potential similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol and drug abuse.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Actimorph.
Repeated use of Actimorph 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 Actimorph 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 Actimorph 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.

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

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.

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 vasoocclusive crisis, close monitoring for ACS symptoms is warranted.

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.

Pre- and postoperative use
Actimorph Orodispersible tablets should be used with caution, pre- and postoperatively, due to the increased risk of ileus or respiratory depression in the postoperative period compared to patients who are not having surgery. Due to the analgesic effect of morphine serious intra-abdominal complications such as bowel perforation can be masked.
Patients who are going to undergo additional procedures to relieve pain (eg plexus block surgery) should not receive Actimorph Orodispersible tablets within 4 hours prior to the intervention. If treatment with Actimorph Orodispersible tablets is indicated, a dose adjustment should be made based on the new post-operative requirements.

Hyperalgesia
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.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased levels of sex hormones and increased prolactin levels
Opioids, such as morphine, may have a pharmacological action on the hypothalamic-pituitary or gonadal axis.
Long-term use of opioid analgesics may be associated with decreased levels of sex hormones and increased prolactin levels. Symptoms include decreased libido, impotence, or amenorrhea.

Concomitant use with rifampicin
Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Oral P2Y12 inhibitor antiplatelet therapy
Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).
Actimorph 20 mg Orodispersible tablets: This medicinal product contains 0.8 microgram benzyl alcohol in each orodispersible tablet.

Benzyl alcohol may cause allergic reactions.

This medicinal product should not be used for more than a week in young children (less than 3 years old).

High quantities should be used with caution and only if necessary, especially in pregnant or breast-feeding women and in subjects with liver or kidney impairment because of the risk of accumulation and toxicity of benzyl alcohol (metabolic acidosis).
This medicinal product contains sulphites.
May rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.
This medicinal product contains morphine, which is listed as a doping substance, and its use can lead to positive results in anti-doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

It must be taken into account that many medicinal products or substances can add their depressant effects of the central nervous system and contribute to decrease vigilance. Medicinal products which depress the CNS include, but are not limited to: other opioids (analgesics, antitussives and substitution treatments), neuroleptics, anxiolytics, sedatives and hypnotics (including benzodiazepines), anxiolytics other than benzodiazepines (eg meprobamate), antiepileptics (including gabapentinoids, e.g., gabapentin or pregabalin), general anaesthetics (including barbiturates), antipsychotics (including phenothiazines), sedative antidepressants (eg amitriptyline, doxepin, mianserine, mirtazapine, trimipramine), sedative H1 antihistamines, muscle relaxants (eg baclofen), thalidomide, central antihypertensives, centrally acting anti-emetics 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.

<u>Concomitant use contraindicated</u>

+ Morphonic agonists-antagonists (eg buprenorphine, nalbuphine, pentazocine)

Mixed agonist/antagonist opioid analgesics should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic as it decreases the analgesic effect by competitive blocking of the receptors, with the risk of appearance of a withdrawal syndrome.

+ Morphic Partial Antagonists (eg Naltrexone, Nalmefene)

Risk of reduction of the analgesic effect.

+ Sodium oxybate

Increased risk of respiratory depression, which can be fatal in case of overdose.

+ Monoamine oxidase inhibitors

MAOIs are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis. Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Concomitant use not recommended

+ Alcohol (drink or excipient)

Alcohol enhancement of the sedative effect of opioid analgesics.

Impaired alertness can make driving dangerous and the use of machinery dangerous.

Since alcohol may enhance the pharmacodynamic effects of Actimorph, concomitant use of alcohol or medicinal products containing alcohol and this medicinal product should be avoided.

+ Sedatives such as benzodiazepines or related medicinal products

The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Combinations subject to precautions for use

+ Rifampicin

Plasma concentrations and efficacy of morphine and its active metabolite may be reduced by rifampicin (see section 4.4). Clinical surveillance and possible adjustment of morphine dose are advisable during and after discontinuation of rifampicin.

+ Other agonist morphine analgesics (alfentanil, codeine, dextromoramide, dihydrocodeine, fentanyl, hydromorphone, oxycodone, pethidine, phenoperidine, remifentanil, sufentanil, tapentadol, tramadol)

Increased risk of respiratory depression, which can be fatal in case of overdose.

+ Morphine-like antitussives (eg dextromethorphan, noscapine, pholcodine)

Increased risk of respiratory depression, which can be fatal in case of overdose.

+ True morphine antitussives (eg codeine, ethylmorphine)

Increased risk of respiratory depression, which can be fatal in case of overdose.

+ Barbiturates (eg allobarbital, amobarbital, bartal, butalbital, butobarbital, hexobarbital, methylphenobarbital, phenobarbital, primidone, secbutabarbital, secobarbital, thiopental, vinbarbital, vinylbital)

Increased risk of respiratory depression, which can be fatal in case of overdose.

+ Other sedative medicinal products
Increase of the central depression. Impaired alertness can make driving dangerous and the use of machinery dangerous.

+ Anticholinergic medicinal products
Medicinal products that block the action of acetylcholine, for example atropine, antihistamines, anti-Parkinson's and anti-emetics, may interact with morphine to potentiate the anticholinergic adverse effects. Significant risk of colonic akinesia, with severe constipation.

+ P2Y12 inhibitors
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.

+ Ritonavir
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.

+ Cimetidine
Cimetidine inhibits the metabolism of morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy
In humans, there are no adequate data available to allow an evaluation of any potential teratogenic risk. There have been reports of a possible link to an increased incident of inguinal hernias. Morphine crosses the placental barrier. Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (see section 5.3). For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.
Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is assured.
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.

Parturition
Morphine can prolong or shorten the duration of labour. Neonates, whose mothers are given opioid analgesics during childbirth, should be monitored for

signs of respiratory depression or withdrawal syndrome and (if necessary), treated with a specific opioid antagonist.

Breast-feeding
Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma. As clinically relevant concentrations may be reached in nursing infants, breast-feeding is not advised.

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

4.7 Effects on ability to drive and use machines

Treatment with Actimorph Orodispersible tablets may cause sedation and it is not recommended that patients drive or use machines if they experience drowsiness. This medicinal product can impair cognitive function and can affect the patient's ability to drive safely mainly at treatment initiation, at any change of dose and in case of association with other central nervous system depressants such as alcohol or sedatives.
When the therapy is stabilized, a general driving ban is not mandatory.

4.8 Undesirable effects

In normal doses, the commonest undesirable effects of morphine are nausea, vomiting, confusion, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with morphine but should they occur the orodispersible tablets can be readily combined with an anti-emetic if required. Constipation however does not stop while continuing the treatment. All these effects are predictable and need to be treated 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).

Systems Organ Classes	Very common	Common	Uncommon	Rare	Very Rare	Not known
Immune system disorders		Hypersensitivity				Anaphylactic reaction Anaphylactoid reaction
Endocrine disorders					Syndrome of inadequate ADH-secretion (SIADH)	

					(symptom: hyponatremia)	
Metabolism and nutrition disorders		Decreased appetite				
Psychiatric disorders	Mood altered, mostly Euphoria but also Dysphoria	Confusion Insomnia Changes in the activity (mostly decreased activity, but also hyperactivity or agitation) Thinking disturbances Cognitive disorders (e.g. hallucinations)			Libido decreased	Drug dependence (see section 4.4) Nightmare (most often in elderly patients)
Nervous system disorders		Dizziness Headache Involuntary muscle contractions Somnolence Dysgeusia	Convulsions Hypertonia Myoclonus (in case of overdose or too fast dose increase in elderly or patients with kidney failure) Paraesthesia Syncope		Tremor	Sedation (dosage dependant) Intracranial pressure increase, which should be treated at first Allodynia Hyperalgesia (see section 4.4) Light-headedness
Eye disorders	Miosis				Nystagmus Blurred vision Double vision (diplopia)	
Ear and labyrinth disorders			Vertigo			
Cardiac disorders			Palpitations Bradycardia Tachycardia			Heart failure
Vascular disorders			Facial flushing Hypotension Hypertension			Hot flushes
Respiratory thoracic and mediastinal disorders			Bronchospasm Pulmonary oedema Respiratory depression (with apnoea at most)		Dyspnoea	Cough reflex decreased Non-cardiogenic pulmonary oedema after rapid dose increase Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Dry mouth Vomiting (notably at treatment initiation) Dyspepsia	Paralytic ileus	Pancreatitis (including exacerbation of pancreatitis)	Intestinal obstruction Dental disease, but a causal relationship to morphine treatment	

					cannot be established.	
Hepatobiliary disorders				Biliary colic		Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders		Rash Hyperhidrosis Urticaria Pruritus				Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, connective tissue and bone diseases					Muscle spasms Muscle rigidity	
Renal and urinary disorders		Urinary retention (notably in case of prostatic adenoma or urethral stenosis)			Renal colic	Ureteric spasm Dysuria
Reproductive system and breast disorders					Amenorrhoea Erectile dysfunction	
General disorders and administration site conditions		Asthenia Fatigue Malaise	Peripheral oedema		Shivers	Drug tolerance Drug withdrawal (abstinence) syndrome Drug withdrawal (abstinence) syndrome neonatal
Investigations			Hepatic enzymes increased			

Description of selected adverse reactions

Drug dependence
Repeated sue of Actimorph can lead to drug dependence, even at therapeutic doses. Téhe risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Withdrawal (abstinence) syndrome:
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

Symptoms

Toxic doses vary considerably with the individual, a single dose can lead to intoxication whereas regular users may tolerate large doses.
Signs of morphine toxicity and overdose are pin-point pupils (miosis), skeletal muscle flaccidity, bradycardia, hypotension, hypothermia, respiratory depression, pneumonia aspiration, somnolence and central nervous system depression which can progress to stupor or coma. Death may occur from respiratory failure. Circulatory failure and deepening coma may occur in more severe cases. Overdose can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.
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.
The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.
In unconscious patients with respiratory arrest, ventilation, intubation and intravenous administration of an opioid antagonist (eg 0.4-2 mg Naloxone i.v.) are indicated.

If respiratory failure persists, the single dose must be repeated 1 to 3 times at three-minute intervals until the respiratory rate is normalized and the patient responds to painful stimuli.
Strict monitoring (at least 24 hours) is necessary because the effect of the opioid antagonist is shorter than that of morphine, so that respiratory insufficiency can be expected to recur.
The dose of the opioid antagonist in children is 0.01 mg per kg body weight per single dose.

Measures to protect against heat loss and for volume therapy may also be 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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, analgesics, opioids, natural opium alkaloid, ATC code: N02A A01

Mechanism of action

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.

Pharmacodynamic effects

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis).

Morphine produces respiratory depression by direct action on brain stem respiratory centres.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

With continued use of morphine, the sensitivity of the CNS to morphine decreases. This habituation can be so pronounced that the patient may require and tolerate high doses of morphine that could be toxic due to respiratory depression if used directly for the first time.

Due to the euphoric effect component of morphine, there is a danger of addiction (see also section 4.4).

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce spasm of the sphincter of Oddi, thus raising intrabiliary pressure.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System
Opioids may affect the hypothalamic pituitary adrenal and hypothalamic pituitary gonadal system resulting in adrenal insufficiency or hypogonadism respectively (see section 4.4).

Other 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

Absorption
Morphine is absorbed relatively quickly after oral administration, mainly from the upper small intestine and also slightly from the stomach. The low absolute bioavailability (20% - 40%) is due to a pronounced first-pass effect. About 20-35% of the circulating morphine binds to plasma proteins, preferably to the albumin fraction.
Distribution
The volume of distribution of morphine is given as 1.0 - 4.7 l/kg after i.v. single administration of 4 – 10 mg. High tissue concentrations are found in the liver, kidney, gastrointestinal tract and muscle. Morphine passes the blood-brain barrier.
Biotransformation
Morphine is metabolized predominantly in the liver but also in the intestinal epithelium. The primary step is the glucuronidation of the phenolic hydroxyl group by hepatic UDP-glucuronyl-transferase and N-demethylation. The main metabolites are mainly morphine-3-glucuronide and, to a lesser extent, morphine-6-glucuronide. Sulfur conjugates and oxidative metabolites such as normorphin, morphine N-oxide and a 2-hydroxylated morphine are also produced. The half-life of glucuronides is significantly longer than that of free morphine. The morphine-6-glucuronide is biologically active. It is possible that a prolonged effect in patients with renal insufficiency is due to this metabolite.
Elimination
Approximately 80% of the administered morphine is found in urine after oral or parenteral administration (10% unchanged morphine, 4% normorphin and 65% glucuronides, of which morphine-3-glucuronide: morphine-6-glucuronide (10:1)). The elimination half-life of morphine is subject to large interindividual fluctuations. In average, it is between 1.7 and 4.5 hours after parenteral administration; occasionally values of around 9 hours were found. About 10% of the morphine glucuronides are excreted via the bile with the faeces.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

Mutagenic and tumorigenic potential

There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans. There have been no long-term animal studies on the tumorigenic potential of morphine.

Reproductive toxicity

Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence).

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Hydroxypropyl cellulose
Microcrystalline cellulose
Crospovidone type A
Acesulfame potassium
Orange flavour (including Benzyl alcohol, Sodium Sulphites)
Silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Polyamide/aluminium/PVC//aluminium-PET perforated unit dose blister
Packs containing 12, 14, 16, 20, 50, 56 and 100 orodispersible tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194, Bureaux de la Colline – Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 06934/0249

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/07/2021

10 DATE OF REVISION OF THE TEXT

30/04/2025