IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0007/044/007
Case No: 2037146

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Boehringer Ingelheim Limited

Ellesfield Avenue, **Bracknell**, **Berkshire RG12 8YS**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Oramorph Unit Dose Vials 10 mg/5 ml

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/08/2007** until **30/01/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oramorph Unit Dose Vials 10 mg/5 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of solution contains 10 mg Morphine Sulphate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Oral solution
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For use in the relief of severe and intractable pain.

4.2 Posology and method of administration

Dosage and administration

Adults: Usual starting dose 10-20 mg (5-10 ml of 10 mg/5 ml Oramorph Unit Dose Vial) every 4 hours.

Children:

Under 5 years: Not recommended.
6-12 years: Maximum dose 5-10 mg (2.5 -5 ml of 10 mg/5 ml Oramorph Unit Dose Vial) every 4 hours.

The dosage can be increased under medical supervision according to the severity of the pain and the patient's previous history of analgesic requirements using Oramorph 30 mg/5 ml UDV or Oramorph 100 mg /5 ml UDV. Reductions in dosage may be appropriate in the elderly and in patients with hepatic or moderate-severe renal impairment, or where sedation is undesirable.

The required dose may be added to a soft drink immediately prior to administration.

When patients are transferred from other morphine preparations to Oramorph Unit Dose Vials, dosage titration may be appropriate. When Oramorph Unit Dose Vials are used in place of parenteral morphine, a 50% to 100% increase in dosage is usually required to achieve the same level of analgesia.

4.3 Contraindications

Respiratory depression, obstructive airways disease, paralytic ileus, known morphine sensitivity, acute hepatic disease acute alcoholism, head injuries, coma, convulsive disorders and where the intracranial pressure is raised. Concurrent administration of monoamine oxidase inhibitors or within two weeks of stopping such treatment.

Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma.

Opioids are contraindicated in acute asthma exacerbations, see section 4.4 for information relating to use in controlled asthma.

4.4 Special warnings and precautions for use

Care should be exercised if morphine sulphate is given in the first 24 hours post operatively, in hypothyroidism, and where there is reduced respiratory reserve, such as kyphoscoliosis, emphysema and severe obesity. Opioids are contraindicated in acute asthma exacerbations. However, it has been suggested that they can be used with caution in controlled asthma.

Morphine sulphate should not be given if paralytic ileus is likely to occur (see section 4.3), or if the patient has bowel or biliary disease. Caution should be exercised where there is an obstructive bowel disorder or prostatic hyperplasia. If constipation occurs this may be treated with the appropriate laxatives.

It is wise to reduce dosage in chronic hepatic and renal disease, myxodema, adrenocortical insufficiency, prostatic hypertrophy or shock.

The administration of morphine may result in severe hypotension in individuals whose ability to maintain homeostatic blood pressure has already been compromised by depleted blood volume or the concurrent administration of drugs such as phenothiazine or certain anaesthetics.

Tolerance and dependence may occur. Withdrawal symptoms may occur on abrupt discontinuation or on the administration of a narcotic antagonist e.g. naloxone.

4.5 Interaction with other medicinal products and other forms of interaction

Phenothiazine antiemetics may be given with morphine, but it should be noted that morphine potentiates the effect of tranquillisers, anaesthetics, hypnotics, sedatives, antipsychotics, tricyclic antidepressants and alcohol. Morphine may possibly increase plasma concentrations of esmolol.

Cimetidine inhibits the metabolism of morphine. Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity. Concomitant use of ritonavir should be avoided as the plasma concentration of morphine may be increased. The absorption of mexiletine may be delayed by concurrent use of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis - please see section 4.3.

4.6 Pregnancy and lactation

Although morphine has been in general use for many years, there is inadequate evidence of safety in human pregnancy and lactation.

Morphine is known to cross the placenta and is excreted in breast milk and may thus cause respiratory depression in the newborn infant. Infants born from mothers who have been taking morphine on a chronic basis may exhibit withdrawal symptoms. This should be borne in mind when considering their use in patients during pregnancy and lactation. Gastric stasis and risk of inhalation pneumonia in mother during labour are increased.

Morphine is not recommended for use during pregnancy and lactation in nursing mothers.

4.7 Effects on ability to drive and use machines

Morphine is likely to impair ability to drive and to use machinery. This effect is even more enhanced when used in combination with alcohol or CNS depressants.

Patients should be warned not to drive or operate dangerous machinery after taking Oramorph.

4.8 Undesirable effects

In routine clinical practice, the commonest side effects of morphine sulphate are nausea, vomiting, constipation, drowsiness and confusion. If constipation occurs, this may be treated with appropriate laxatives.

Other adverse reactions include:

Cardiovascular:

Bradycardia, tachycardia, palpitations, orthostatic hypotension and hypothermia. Raised intracranial pressure occurs in some patients.

Central Nervous system:

Headache, restlessness**,** vertigo, mood changes, hallucinations, dependence, muscle rigidity.

Gastrointestinal:

Dry mouth, biliary spasm.

Genitourinary:

Decreased libido/potency, micturition may be difficult and there may be ureteric spasm. There is also an antidiuretic effect.

General:

Sweating, facial flushing and miosis.

These effects are more common in ambulant patients than in those who are bedridden.

As a consequence of histamine release, urticaria and or pruritus may occur in some individuals.

4.9 Overdose

Signs of morphine toxicity and overdosage:

These are likely to consist of pin-point pupils, respiratory depression and hypotension. Circulatory failure and deepening coma may occur in more severe cases. Convulsions may occur in infants and children. Death may occur from respiratory failure.

Treatment of morphine overdosage:

Administer naloxone 0.4-2 mg intravenously. Repeat at 2-3 minute intervals as necessary, to a maximum of 10 mg, or by an infusion of 2 mg in 500 ml of normal saline or 5 % dextrose (4 micrograms/ml). Empty the stomach. A 0.02 % aqueous solution of potassium permanganate may be used for lavage. Care should always be taken to ensure that the

airway is maintained. Assist respiration if necessary. Maintain fluid and electrolyte levels, oxygen, i.v. fluids, vasopressors and other supportive measures should be employed as indicated.

Caution: the duration of the effect of naloxone (2-3 hours) may be shorter than the duration of the effect of the morphine overdose. It is recommended that a patient who has regained consciousness after naloxone treatment should be observed for at least 6 hours after the last dose of naloxone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Morphine binds to opiate receptors located on the cell surfaces of the brain and nervous tissue. This action results in alteration of neurotransmitter release and calcium uptake. It has been postulated that this is the basis of the modulation of sensory input from afferent nerves sensitive to pain.

5.2 Pharmacokinetic properties

Morphine N-methyl ^{14}C sulphate administered orally to humans reaches a peak plasma level after around 15 minutes: levels of plasma-conjugated morphine peak at about 3 hours, and slowly decrease over the following 24 hours. After the first hour no significant differences in total plasma levels of radioactivity are seen whether administration is by intravenous, intramuscular, subcutaneous or oral route.

Morphine is a basic amine, and rapidly leaves the plasma and concentrates in the tissues. In animals it has been shown that a relatively small amount of free morphine crosses the blood-brain barrier. Morphine is metabolised in the liver and probably also in the mucosal cells of the small intestine. The metabolites recovered in the urine, in addition to free morphine, are morphine-3-glucuronide and morphine ethereal sulphate. These account for over 65 % of administered radioactivity; further radioactivity can be recovered as exhaled $^{14}CO_2$.

5.3 Preclinical safety data

No further relevant preclinical data are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Disodium edetate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25 °C. Keep container in outer carton.

6.5 Nature and contents of container

Marketed packs:
5 ml low density polyethylene Unit Dose Vials packed into cartons containing 20 vials.

Non-marketed packs:
Cartons containing 30, 50, 60, or 100 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Not for parenteral use.
Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Ltd.
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS
UK

8 MARKETING AUTHORISATION NUMBER

PA 7/44/7

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 April 1992

Date of last renewal: 31 January 2004

10 DATE OF REVISION OF THE TEXT

August 2007