Boehringer Ingelheim

09 OCT 2019

Boehringer Ingelheim Limited · Ellesfield Avenue, Bracknell, Berkshire RG12 8YS

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8 October 2019

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Dear Ms. Schofield,

Re: Inquest into the death of George Benjamin RIMMER

Thank you for your letter of 16th August 2019 (received 21st August 2019) in relation to the above inquest. We are very sorry to hear about the death of this gentleman and thank you for the opportunity to review the provision of Oramorph® Oral Solution 10 mg/5 ml (Oramorph®) to ensure optimal information is provided to patients.

Boehringer Ingelheim Limited (BIL) takes the safety of our medicines extremely seriously and ensures compliance with all regulations with respect to the monitoring of safety, packaging, labelling and provision of information to healthcare professionals (via the Summary of Product Characteristics [SmPC] and patients (via the Patient Information Leaflet [PIL]).

Changes have recently been made to the Oramorph® SmPC (ref 1) and PIL as a result of the European Medicine Agency (EMA) review of the Periodic Benefit Risk Evaluation Report (PBRER) for Oramorph® submitted by BIL in 2018. It should be noted that the EMA reviewed the PBRER's for all medicines containing the active ingredient morphine at this time, with many of their recommendations intended to provide consistency in warnings associated with the active ingredient (morphine) across all these medicines. BIL complied with all EMA recommendations and submitted them to the United Kingdom (UK) Regulatory Agency, the Medicines and Healthcare products Regulatory Agency (MHRA), who granted approval for the updated text on 19th December 2018. The PIL version for this update was dated November 2018. There has been a subsequent update to the November 2018 PIL

reflecting an administrative change only in preparation for BREXIT. The current PIL date is therefore March 2019 (ref 2).

In addition, following a request by the MHRA to the manufacturers of opioid containing medicines in a letter dated 7th May 2019, the outer carton labelling (ref 3) and bottle label (ref 4) have been updated to contain the following boxed statement:

Can cause addiction Contains opioid

These changes were approved by MHRA for Oramorph® Oral Solution on 18th June 2019 and are the only recent non-administrative change to the carton and bottle labelling.

In responding to your letter of 16th August 2019, we have, as requested, addressed the 7 "matters of concern", describing already completed or proposed actions with associated timeline or explained why we have taken no action.

We have referred to the current versions of the PIL (March 2019), outer carton (May 2019) and bottle labelling (May 2019) and also the versions supplied with the Oramorph® product that we believe would have been dispensed to Mr Rimmer. The PIL provided to Mr Rimmer inside the Oramorph® pack we assume to be the June 2015 PIL (ref 5) version. For your convenience, we have also included with this letter the June 2015 PIL, marked with annotations of the changes made in the update to the November 2018 PIL version (ref 6), which is identical in wording to the current (March 2019) PIL except for the name of the Marketing Authorisation Holder. These changes in the PIL from June 2015 can be summarised as follows:

Changes from June 2015 to November 2018 PIL:

- Addition of a warning to check the suitability of taking Oramorph® if previously addicted to drugs or alcohol.
- Addition of 'increased sensitivity to pain' as a side effect and in general a re-ordering of the side effects section.
- Addition of wording on the risk of pneumonia from an overdose and symptoms this may cause.
- Revised wording in the warnings and precautions regarding low cortisol, changes in sex hormone levels, dependency and withdrawal symptoms.

- Revised wording of the risk of taking Oramorph® with other sedative medicines.
- Revised wording in the risk of newborn withdrawal if taking Oramorph® in pregnancy.
- Revised wording warning of withdrawal and associated symptoms.
- Updated adverse event reporting details.

Changes from November 2018 to March 2019 PIL:

- Change in Marketing Authorisation Holder in light of preparations for BREXIT.

You will see in our responses to the 7 "matters of concern" that whilst we do consider the PIL, outer carton and bottle labelling versions both now and as supplied with the Oramorph® Mr Rimmer received, provide sufficient information to address your concerns, we have proposed one additional change to each of these documents. These changes are outlined below and also summarised on page 9.

1. **Mr Rimmer was known to swig out of the bottle rather than take a measured dose as most patients do.**

We view this matter of concern as more pertinent to Mr Rimmer's prescribing clinician and other healthcare professionals.

As per *Good Medical Practice* (2013) (ref 7) and *Good practice in prescribing and managing medicines and devices* (2013) (ref 8) it is the responsibility of the prescribing clinician to ensure that he/she provides an explanation to the patient of how and when to take the medicine and how to adjust the dose if necessary. It is also the expectation that the prescribing clinician describes the likely benefits, risks and burdens, including serious and common side effects of any treatment provided. Our view is that guidance provided in *Good Medical Practice* and *Good practice in prescribing and managing medicines and devices* is particularly relevant when also considering matters of concern 2, 3 and 4 as listed in your report.

The PIL is provided to supplement the instructions given by the prescribing clinician. The Oramorph® PIL (both current and the presumed June 2015 version that Mr Rimmer received) provides clear instruction to the patient that the dose of Oramorph® should be measured using a 5ml spoon (see also the response to matters of concerns numbers 2 and 6).

Conclusion 1)
We took no specific action in response to this particular matter of concern. However please see our response to matter of concern 6, which is closely related.

2. Mr Rimmer self medicated as required.

As mentioned in point 1 above, in relation to *Good Medical Practice,* we view this as a matter of concern more pertinent to Mr Rimmer's prescribing clinician and other healthcare professionals involved in his care rather than BIL.

We have carefully reviewed the current and June 2015 version of the PIL and consider both versions provide clear instruction on the intended dosing (amount and frequency) in the section entitled 'HOW MUCH TO TAKE' by the reminding the patient:

- to take this "..exactly as the doctor has told you"
- the maximum dose is 5 to 10mls (one to two teaspoons)
- to check with their doctor or pharmacist if they are not sure.

3. HOW TO TAKE ORAMORPH ORAL SOLUTION

Always take this medicine exactly as your doctor has told you
You should check with your doctor or pharmacist if you are not sure

Taking this medicine
- Take this medicine by mouth only
- Use a 5 ml plastic spoon to measure your dose
- They are available from your pharmacist

How much to take
Your doctor will decide the amount of medicine to give you

Adults
- The most that should be taken is 5 to 10 ml (one to two teaspoons) every four hours

This section also included a statement not to take more than is prescribed and to discuss with a doctor if the prescribed dose is no longer effective.

Your body may get used to the medicine (tolerance)
- Do not take more than your doctor has prescribed
- If you have been taking your medicine for some time you may find that it does not seem to be working as well as it did If this happens, talk to your doctor

Conclusion 2)
Given the clear instructions in the current PIL (unchanged from the June 2015 version) to take the recommended dose and to seek advice if the prescribed dose is no longer effective, we took no specific action in response to this matter of concern.

3. **Mr Rimmer's GP did not recall advising him of the possible consequences of exceeding the prescribed dose.**

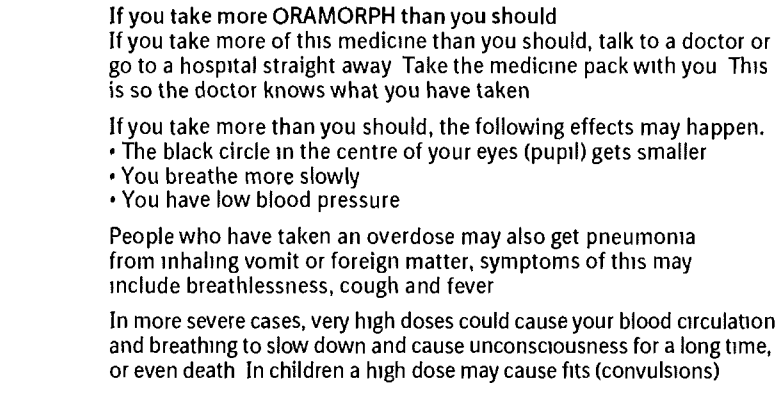
We view this point to be directed to Mr Rimmer's prescribing clinician and other healthcare professionals involved in his care rather than BIL. However, as discussed in relation to matters of concern 4 and 5, we do have clear warnings in the PIL of the consequences (symptoms, signs and risks) if more than the prescribed dose is taken.

Conclusion 3)
We took no specific action in response to this matter of concern.

4. **There was no evidence to show that anyone had counselled Mr Rimmer with regards to the use of this drug.**

Whilst similarly we view this matter of concern as relevant to Mr Rimmer's prescribing clinician and other healthcare professionals involved in his care, we would like to point out that both the current (and also June 2015) PIL contain clear wording regarding:

- advice to seek medical help in case the patient took "more ORAMORPH than you should"
- specific guidance / warning as to symptoms and signs they may notice
- the risk of taking too much including in severe cases, unconsciousness and death.



If you take more ORAMORPH than you should
If you take more of this medicine than you should, talk to a doctor or go to a hospital straight away Take the medicine pack with you This is so the doctor knows what you have taken

If you take more than you should, the following effects may happen.
• The black circle in the centre of your eyes (pupil) gets smaller
• You breathe more slowly
• You have low blood pressure

People who have taken an overdose may also get pneumonia from inhaling vomit or foreign matter, symptoms of this may include breathlessness, cough and fever

In more severe cases, very high doses could cause your blood circulation and breathing to slow down and cause unconsciousness for a long time, or even death In children a high dose may cause fits (convulsions)

Please note: In the extract of the wording of the current PIL (March 2019) shown in the screenshot above, the identical wording was used in the June 2015 PIL, save that the third paragraph "*People who.....cough and fever*" was added in this later version.

Conclusion 4

We feel the wording of the PIL (both current and June 2015 version) is sufficient to warn the patient of the need to take only the dose the doctor has prescribed, to seek medical help if too much is taken and the warning signs/symptoms and associated risks of taking too much and therefore we took no further action to this matter of concern.

5. **The leaflet that comes with the bottle does not provide a sufficient warning of the dangers of taking an excess dose.**

We would like to refer to our answer to matter of concern 4). The section of the PIL entitled 'If you take more ORAMORPH than you should', provides warnings and a clear instruction on what to do in the event of taking more than the doctor prescribed. This section also provides explicit information about the dangers of taking an excess dose including the risk of death.

Conclusion 5
Having reviewed the current and June 2015 version wording in light of your letter, we feel the PIL sufficiently warns of the dangers of taking an excess dose. Therefore, we took no further action in response to this matter of concern.

6. **There is no mention of the dangers of drinking from the bottle and not measuring the dose.**

The 'HOW TO TAKE ORAMORPH ORAL SOLUTION' section of the PIL gives clear instructions on how to administer Oramorph®, by mouth, using a 5ml spoon (available from a pharmacist) with the maximum dose being one to two teaspoons every four hours.

We also understand it to be good dispensing practice that a pharmacist ensures any solution has a measuring spoon (or alternative device) provided.

3. HOW TO TAKE ORAMORPH ORAL SOLUTION

Always take this medicine exactly as your doctor has told you
You should check with your doctor or pharmacist if you are not sure

Taking this medicine
- Take this medicine by mouth only
- Use a 5 ml plastic spoon to measure your dose
- They are available from your pharmacist

How much to take
Your doctor will decide the amount of medicine to give you

Adults
- The most that should be taken is 5 to 10 ml (one to two teaspoons) every four hours

Whilst there is no explicit warning in the PIL not to drink directly from the bottle, the wording of the 'HOW TO TAKE ORAMORPH ORAL SOLUTION' is also consistent with other oral morphine solutions (ref 9, 10) available in the UK. These also provide specific instructions about measuring the correct dose but, like Oramorph®, they do not have an explicit warning not to drink directly from the bottle.

The Oramorph® PIL, the SmPC, bottle and carton labelling, has been approved by the relevant regulatory authority in the UK, the MHRA, and in our view, meets their requirements as to the information that must be provided to patients.

However, we will propose to the MHRA that we include within the 'HOW TO TAKE ORAMORPH ORAL SOLUTION' section the following statement (or words to that effect to be agreed with the MHRA):

> *'Do not drink directly from the bottle as this may result in you taking the incorrect dose (too little or too much). Drinking from the bottle can result in an overdose with potential for harmful effects including, but not limited to, pneumonia, low blood pressure, unconsciousness and even death.'*

Conclusion 6
We believe the PIL wording is clear and of note, is consistent with other providers of oral morphine solution [ref 9,10]. However, we will request to the MHRA that we add to the PIL an explicit warning statement not to drink directly from the bottle, additionally with text highlighting the risks of doing so, so mirroring the points made in the text explaining the consequences of taking too much, as referred to in matter of concern 4.

7. **There is no warning on the bottle to act as a reminder of the dangers of taking an excess dose or of the cumulative effect of taking more than the prescribed amount.**

Please be aware the space to include additional information on the bottle label is limited and guidance to the patient is covered in detail in the PIL (see response to matter of concern 4 confirming that the warning symptoms /signs and risks of an excess dose, including death, are clearly stated).

The bottle and outer carton labelling both currently has the following statement *"To be taken as directed by the prescriber"*.

We consider this statement to clearly instruct the patient to follow the advice of the clinician and is in line with statutory requirements for medicines supplied on prescription.

As mentioned in our response to matter of concern 6, the SmPC, PIL and outer carton and bottle labelling for Oramorph® have been reviewed and approved by the MHRA, meeting required standards.

However, we propose to strengthen and emphasise the wording on both the bottle label and carton label:

- From 'To be taken as directed by the prescriber'
- To **'Must only be taken as directed by the prescriber'**, emboldening the font in this revision, to ensure prominence of the wording to the patient.

Conclusion 7
We believe the current bottle and carton labelling wording is sufficiently clear. However, we will request to the MHRA that we amend the wording and embolden for emphasis the statement regarding "..taken as directed by the prescriber".

Summary of BIL proposed actions:

We have proposed three new actions, as summarised below:

1. **Change to PIL**

We propose to add the following wording (or words to that effect) to the 'HOW TO TAKE ORAMORPH ORAL SOLUTION' section:

'Do not drink directly from the bottle as this may result in you taking the incorrect dose (too little or too much). Drinking from the bottle can result in an overdose with potential for harmful effects including, but not limited to, pneumonia, low blood pressure, unconsciousness and even death.'

2. **Change to the bottle label**

We propose to **amend** the bottle label (in case the patient misplaces the outer carton and/or PIL):

- From: 'To be taken as directed by the prescriber'
- To: **'Must only be taken as directed by the prescriber'**

We further propose the amended text will be emboldened for emphasis.

3. **Change to outer carton labelling**

Similar to above, we propose to amend the statement on the outer carton:

- From: 'To be taken as directed by the prescriber'
- To: **'Must only be taken as directed by the prescriber'**
  (text will be emboldened for emphasis).

Please be advised that any proposed additions and amendments to the PIL, bottle and outer carton labelling will need to be reviewed and approved by both the MHRA (UK) and the Healthcare and Products Regulatory Agency (HPRA) in Ireland, since we maintain a joint pack for both countries.

We will, as part of the submission of these proposed changes to the regulatory authorities in both the UK and Ireland, provide the MHRA and HPRA with your letter (redacted for the patient's name) so they are aware of the background for our proposed changes. We undertake to submit these changes to the MHRA and HPRA no later than the end of December 2019.

We trust that we have adequately addressed the maters of concern that you have raised, but should there be anything further you require, please do not hesitate to let me know.

Yours sincerely,

Uday Bose
Country Managing Director

References

Please note that references 1-6 are provided in hard copy with this letter. All other references can be found at the website address provided.

1. Summary of Product Characteristics (SmPC)
   Oramorph Oral Solution 10 mg/5 ml (Oramorph®)
   – current version, revision of text March 2019
   https://www.medicines.org.uk/emc/product/902/smpc

2. Patient Information Leaflet (PIL)
   Oramorph Oral Solution 10 mg/5 ml (Oramorph®)
   – current version, updated March 2019
   https://www.medicines.org.uk/emc/product/902/pil

3. Artwork for the outer carton (300ml bottle as example)
   Oramorph Oral Solution 10 mg/5 ml (Oramorph®)
   – current version, updated May2019

4. Artwork for the bottle label (300ml bottle as example)
   Oramorph Oral Solution 10 mg/5 ml (Oramorph®)
   – current version, updated May 2019

5. Patient Information Leaflet (PIL)
   Oramorph Oral Solution 10 mg/5 ml (Oramorph®)
   – version June 2015

6. Annotated version of the June 2015 PIL with the changes which were included in the November 2018 update.

7. "Good Medical Practice", General Medical Council, published 25 March 2013
   https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-medical-practice

8. "Good practice in prescribing and managing medicines and devices", General Medical Council, updated March 2013
   https://www.gmc-uk.org/-/media/documents/Prescribing_guidance.pdf_59055247.pdf

9. Patient Information Leaflet (PIL)
   Morphine Sulfate 10mg/5ml Oral Solution, Wockhardt UK Ltd
   https://www.medicines.org.uk/emc/product/2629/pil

10. Patient Information Leaflet (PIL)
    Morphine Sulfate 10mg/5ml Oral Solution, Martindale Pharma
    https://www.medicines.org.uk/emc/product/3427/pil

Oramorph Oral Solution

Summary of Product Characteristics Updated 08-Apr-2019 | Boehringer Ingelheim Limited

1. Name of the medicinal product

Oramorph Oral Solution 10 mg/5 ml

2. Qualitative and quantitative composition

Each 5 ml of Oramorph Oral Solution contains 10 mg of Morphine Sulfate

Excipient(s) with known effect Each 5 ml also contains 1500 mg sucrose, 0 525 ml Ethanol (96%), 9 mg methyl parahydroxybenzoate (E218) and 1 mg propyl parahydroxybenzoate (E216)

For full list of excipients, see Section 6 1

3. Pharmaceutical form

Oral solution

A clear, colourless oral solution

4. Clinical particulars

4.1 Therapeutic indications

For the relief of severe pain in adults, adolescents (aged 13-18 years) and children (aged 1-12 years)

4.2 Posology and method of administration

Posology

Adults	Recommended dose 10-20 mg (5-10 ml) every 4 hours
	Maximum daily dose 120 mg per day

Paediatric population

Children 13-18 years	Recommended dose 5-20 mg (2 5 – 10 ml) every 4 hours
	Maximum daily dose 120 mg per day
Children 6-12 years	Recommended dose 5-10 mg (2 5-5 ml) every 4 hours
	Maximum daily dose 60 mg per day
Children 1-5 years	Recommended dose 5 mg (2 5 ml) every 4 hours
	Maximum daily dose 30 mg per day
Children under 1 year	Not recommended

Dosage can be increased under medical supervision according to the severity of the pain and the patient's previous history of analgesic requirements

Special populations

Reductions in dosage may be appropriate in the elderly and in patients with chronic hepatic disease (for acute hepatic disease see section 4 3), renal impairment, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, shock or where sedation is undesirable

Discontinuation of therapy

An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued Therefore the dose should be gradually reduced prior to discontinuation

Method of Administration

For oral use

When patients are transferred from other morphine preparations to Oramorph Oral preparations dosage titration may be appropriate

Morphine sulfate is readily absorbed from the gastro-intestinal tract following oral administration However, when oral

Oramorph preparations are used in place of parenteral morphine, a 50 % to 100 % increase in dosage is usually required in order to achieve the same level of analgesia

4.3 Contraindications

Oramorph is contraindicated in

- patients known to be hypersensitive to morphine sulfate or to any other component of the product
- respiratory depression
- obstructive airways disease
- paralytic ileus (see section 4 4)
- acute hepatic disease
- acute alcoholism
- head injuries (see section 4 4)
- coma (see section 4 4)
- increased intracranial pressure (see section 4 4)
- convulsive disorders
- patients with known morphine sensitivity
- concurrent administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use (see section 4 5)
- patients with phaeochromocytoma Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release
- 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 sulfate is given

- in the first 24 hours post-operatively,
- in hypothyroidism (see section 4 2),
- and where there is reduced respiratory function, such as kyphoscoliosis, emphysema, cor pulmonale and severe obesity

Asthma

It has been suggested that opioids can be used with caution in controlled asthma However, opioids are contraindicated in acute asthma exacerbations (see section 4 3)

Head injury and increased intracranial pressure

Oramorph is contraindicated in patients with increased intracranial pressure, head injuries and coma (see section 4 3) The capacity of morphine to elevate cerebrospinal fluid pressure may be greatly increased in the presence of already elevated intracranial pressure produced by trauma Also, morphine may produce confusion, miosis, vomiting and other adverse reactions which may obscure the clinical course of patients with head injury

Abdominal conditions

Morphine sulfate must not be given if paralytic ileus is likely to occur (see section 4 3), or if the patient has bowel or obstructive biliary disease Should paralytic ileus be suspected or occur during use, Oramorph should be discontinued immediately

Caution should be exercised where there is an obstructive bowel disorder, biliary colic, operations on the biliary tract, acute pancreatitis or prostatic hyperplasia

If constipation occurs this may be treated with the appropriate laxatives

Care should be exercised in patients with inflammatory bowel disease

Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions and complications following abdominal surgery

Hypotensive effect

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 (see section 4 5)

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance The risk increases with the time the drug is used, and with higher doses Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine For individual symptoms, see section 4 8

Abuse

Morphine sulfate is an opioid agonist and controlled drug Such drugs are sought by drug abusers and people with addiction disorders Morphine sulfate can be abused in a manner similar to other opioid agonists, legal or illicit This should be considered when prescribing or dispensing morphine in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion Morphine should be used with particular care in patients with a history of alcohol and drug abuse

Morphine sulfate may be abused by inhaling or injecting the product These practices pose a significant risk to the abuser that could result in overdose and death

Hypersensitivity

Hypersensitivity and anaphylactic reactions have both occurred with the use of Oramorph Care should be taken to elicit any history of allergic reactions to opiates Oramorph is contraindicated in patients known to be hypersensitive to morphine sulfate (see section 4 3)

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 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 amenorrhoea

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

Risk in special populations

Morphine is metabolised by the liver and should be used with caution in patients with hepatic disease as oral bioavailability may be increased It is wise to reduce dosage in chronic hepatic and renal disease, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy or shock (see section 4 2)

The active metabolite Morphine-6-glucuronide may accumulate in patients with renal failure, leading 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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Oramorph Oral Solution and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death

Because of these risks, co-prescription of Oramorph Oral Solution and sedative medicines should be reserved for patients for whom alternative treatment options are not possible

Oramorph Oral Solution particularly when prescribed concomitantly with sedative medicines, should be used at the lowest effective dose for the shortest period of time

Patients should be monitored 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)

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

Excipient related warnings

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine

Oramorph Oral Solution contains the excipients methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed)

Oramorph Oral Solution contains 10 vol % ethanol (alcohol) Each dose contains up to 0 81 g of alcohol which is equivalent to 20 ml beer or 8 3 ml wine Harmful for those suffering from alcoholism To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis, therefore their concomitant use with Oramorph is contraindicated (see section 4 3)

Gabapentin

Interactions have been reported in those taking morphine and gabapentin Reported interactions suggest an increase in opioid adverse events when co-prescribed, the mechanism of which is not known Caution should be taken where these medicines are co-prescribed

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately

Ritonavir

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir may increase the activity of glucuronyl transferases Consequently, co-administration of ritonavir and morphine may result in decreased serum concentrations of morphine with possible loss of analgesic effectiveness

Rifampicin

Rifampicin can reduce the plasma concentration of morphine and decrease its analgesic effect, the mechanism of which is not known

Cimetidine

Cimetidine inhibits the metabolism of morphine

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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)

Other CNS depressants

It should be noted that morphine potentiates the effects of CNS depressants such as tranquillisers, anaesthetics (see section 4 4), hypnotics, sedatives, antipsychotics, tricyclic antidepressants and alcohol

Esmolol

Morphine may increase plasma concentrations of esmolol

Domperidone/metoclopramide

Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity

Mexiletine

The absorption of mexiletine may be delayed by concurrent use of morphine

Phenothiazine antiemetics

Phenothiazine antiemetics may be given with morphine However, hypotensive effects have to be considered (see section 4 4)

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Morphine is known to cross the placenta Therefore, Oramorph should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh any possible risk to the foetus

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

The risk of gastric stasis and inhalation pneumonia is increased in the mother during labour Since morphine rapidly crosses the placental barrier it should not be used during the second stage of labour or in premature delivery because of the risk of secondary respiratory depression in the newborn infant

The quantity of ethanol contained in Oramorph Oral Solution should be considered in pregnant women (See section 4 4)

Breast-feeding

Although morphine sulfate has been in general use for many years, there is inadequate evidence of safety during lactation

Morphine is not recommended for nursing mothers Morphine is excreted in breast milk, and may thus cause respiratory depression in the newborn infant

Fertility

Long term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women This is thought to be dose related and can lead to amenorrhoea, reduced libido, infertility and erectile dysfunction

Animal studies have shown that morphine may reduce fertility (see 5 3 preclinical safety data)

4.7 Effects on ability to drive and use machines

Morphine sulfate 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

This medicine can impair cognitive function and can affect a patient's ability to drive safely This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988 When prescribing this medicine, patients should be told

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

4.8 Undesirable effects

Data from clinical trials are not available Therefore all frequencies of the undesirable effects are unknown

In normal doses, the commonest side effects of morphine sulfate are nausea, vomiting, constipation, drowsiness and confusion If constipation occurs, this may be treated with appropriate laxatives The effects of morphine have led to its abuse and misuse Dependence and addiction may develop with regular, inappropriate use

A full list of currently known adverse reactions is presented below

SOC Category	Side effect
Immune system disorders	Hypersensitivity Anaphylactic reaction (see section 4 4) Anaphylactoid reactions
Psychiatric disorders	Confusional state Restlessness

	Altered mood Hallucination Dependence (see section 4 4)
Nervous system disorders	Somnolence Headache Increased intracranial pressure (see section 4 4) Allodynia Hyperalgesia (see section 4 4)
Eye Disorders	Miosis
Ear and labyrinth disorders	Vertigo
Respiratory, thoracic and mediastinal disorders	Respiratory depression (see section 4 4 and section 4 6)
Cardiac disorders	Bradycardia Tachycardia Palpitations
Vascular disorders	Hypotension Flushing
Gastrointestinal disorders	Nausea Vomiting Constipation (see section 4 4) Dry mouth
General disorders and administration site conditions	Hypothermia Drug tolerance (see section 4 4) Drug withdrawal (abstinence) syndrome (see section 4 4 and section 4 6)
Hepatobiliary Disorders	Biliary colic
Skin and subcutaneous tissue disorders	Urticaria Pruritus Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle rigidity
Renal and unnary disorders	Dysuria Ureteral spasm Oliguria
Reproductive system and breast disorders	Decreased libido Erectile dysfunction

Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance 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 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

Yellow Card Scheme

Website: www mhra gov uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms

Signs of morphine toxicity and overdosage are likely to consist of pin-point pupils, respiratory depression and hypotension Circulatory failure, pneumonia aspiration and deepening coma may occur in more severe cases Convulsions may occur in infants and children Death may occur from respiratory failure

Treatment

Adults Administer 0 4-2 mg of naloxone intravenously Repeat at 2-3 minute intervals as necessary to a maximum of 10 mg, or by 2 mg in 500 ml of normal saline or 5 % dextrose (4 micrograms/ml) Children 5-10 micrograms per kilogram body weight intravenously If this does not result in the desired degree of clinical improvement, a subsequent dose of 100 mcg/kg body weight may be administered

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 Peak plasma concentrations of morphine are expected to occur within 15 minutes of oral ingestion Therefore gastric lavage and activated charcoal are unlikely to be beneficial

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

Pharmacotherapeutic group Natural opium alkaloids ATC code NO2AA01

Morphine binds to specific receptors which are located at various levels of the central nervous system and also in various peripheral organs The pain sensation and the affective reaction to pain is relieved by interaction with the receptors in the central nervous system

5.2 Pharmacokinetic properties

Absorption

Morphine is modestly absorbed from the gastrointestinal tract following oral administration Following oral administration of radiolabelled morphine to humans, peak plasma levels were reached after approximately 15 minutes Morphine undergoes significant first pass metabolism in the liver resulting in a systemic bioavailability of approximately 25%

Distribution

Approximately one third of morphine in the plasma is protein bound after a therapeutic dose

Biotransformation

Metabolism of morphine principally involves conjugation to morphine 3- and 6- glucuronides Small amounts are also metabolised by N-demethylation and N-dealkylation Morphine-6-glucuronide has pharmacological effects indistinguishable from those of morphine The half-life of morphine is approximately 2 hours The t1/2 of morphine-6-glucuronide is somewhat longer

Elimination

A small amount of a dose of morphine is excreted through the bowel into the faeces The remainder is excreted in the urine, mainly in the form of conjugates Approximately 90 % of a single dose of morphine is excreted in the first 24 hours Enterohepatic circulation of morphine and its metabolites can occur, and may result in small quantities of morphine to be present in the urine or faeces for several days after the last dose

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients

Ethanol (96%), corn syrup, sucrose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and purified water

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years

Discard Oramorph Oral Solution 3 months after first opening

6.4 Special precautions for storage

Do not store above 25°C Store in the original container to protect from light

6.5 Nature and contents of container

Amber glass bottles with a tamper–evident, child resistant polypropylene closure with expanded PE liner are available in packs of 100 ml, 250 ml, 300 ml or 500 ml

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

None stated

7. Marketing authorisation holder

Boehringer Ingelheim International GmbH

Binger Strasse 173

55216 Ingelheim am Rhein

Germany

8. Marketing authorisation number(s)

PL 14598/0114

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation 8th March 1988

Date of last renewal 30th June 2005

10. Date of revision of the text

March 2019

Company Contact Details

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Ref 2.

Oramorph® Oral Solution 10 mg/5 ml

Boehringer Ingelheim

437737/GB/17

(morphine sulfate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORAMORPH ORAL SOLUTION IS AND WHAT IT IS USED FOR

The name of your medicine is ORAMORPH Oral Solution 10 mg/5 ml (called ORAMORPH in this leaflet)
- It contains a medicine called morphine sulfate. This belongs to a group of medicines called 'opioid analgesics'.
- It is used to relieve severe pain.

2. BEFORE YOU TAKE ORAMORPH ORAL SOLUTION

Do not take ORAMORPH if:
- You are allergic (hypersensitive) to morphine sulfate or any of the other ingredients of ORAMORPH (listed in Section 6 below).
- You have problems with your lungs or breathing such as 'hypoventilation' or 'Chronic Obstructive Pulmonary Disease' (COPD).
- You are having an asthma attack.
- You have sudden or recent liver problems.
- You have recently had a head injury.
- You have something called 'phaeochromocytoma'. This is a rare tumour which is not malignant.
- You have fits (convulsions) or increased pressure inside your skull.
- The person taking the medicine is in a deep and prolonged unconscious state (coma).
- You are addicted to alcohol or have recently consumed large amounts of alcohol.
- You are taking or have in the last two weeks taken medication to treat depression such as monoamine-oxidase inhibitors (MAOIs).
- You have paralytic ileus (loss of intestinal movement).

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Take special care with ORAMORPH
Check with your doctor or pharmacist before taking your medicine if
- You are pregnant, trying to become pregnant or if you are breast-feeding.
- You have had an operation within the last 24 hours.
- You have a particular lung problem that causes shortness of breath called emphysema or you have heart failure.
- You have shock (circulatory failure).
- You have asthma.
- You have gall bladder problems.
- You have long term (chronic) liver or kidney problems.
- You are a man who has prostate problems.
- You have an under-active thyroid gland or swelling of your skin (myxoedema).
- Your spine is unusually curved (kyphoscoliosis).
- You have bowel problems.
- You have an under-active adrenal gland (adrenocortical insufficiency).
- You are very overweight.
- You have once been dependent on drugs or alcohol.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking ORAMORPH.

Warnings and precautions
Talk to your doctor, nurse or pharmacist if you experience any of the following symptoms while you are taking ORAMORPH
- Increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in strong analgesic ("painkiller").
- Weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of your adrenal glands producing too little of a hormone called cortisol, and you may need to take a hormone supplement.
- Loss of libido (sex drive), difficulty getting an erection, menstrual periods stopping. This may be because of your body producing less sex hormones.
- You feel that you are becoming dependent on ORAMORPH while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for the pain. This is particularly important to look out for if you have once been dependent on drugs or alcohol.
- Withdrawal symptoms. The most common withdrawal symptoms are mentioned in section 3. If this occurs, your doctor may change the type of medicine or the times between doses.

Other medicines and ORAMORPH
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because ORAMORPH can affect the way some other medicines work. Also some other medicines can affect the way ORAMORPH works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines
- Medicines to help you sleep, make you feel less anxious or calm you down such as tranquilisers, hypnotics, sedatives, antipsychotics or tricyclic antidepressants
  - Taking ORAMORPH together with sedative medicines such as benzodiazepines or related medicines increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, taking ORAMORPH together with these types of medicines should only be considered when other treatment options are not possible. However if your doctor does prescribe ORAMORPH together with sedative medicines the dose and duration of taking the treatments together should be limited by your doctor.
  - Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor if you experience these symptoms.
- Anaesthetics - used during operations
- Domperidone, metoclopramide or phenothiazine - medicines for feeling sick (nausea) and being sick (vomiting)
- Mexiletine and esmolol - for controlling heart rhythm
- Ritonavir - for HIV infections
- Cimetidine - for stomach ulcers, indigestion or heartburn
- Monoamine oxidase inhibitors (MAOIs) - for depression
- Rifampicin - used to treat tuberculosis and other infections
- Gabapentin - for epilepsy and long lasting pain caused by damage to the nerves

Taking ORAMORPH with food and drink
You should avoid alcohol whilst taking this medicine.

Pregnancy and breast-feeding
Talk to your doctor before taking this medicine if you are pregnant, trying to become pregnant or if you are breast-feeding. If you take this medicine during pregnancy or while breast-feeding, it may slow down the baby's breathing. If you take this medicine for a long time whilst pregnant, it may mean that the baby will be born showing signs of withdrawal, which should be treated by a doctor.

Operations and anaesthetics
Tell your doctor or pharmacist if you are due to have an operation or an anaesthetic or if you have had an operation or an anaesthetic within the last 24 hours.

Driving and using machines
You may feel drowsy while taking this medicine. If this happens, do not drive or use any tools or machines.

Additional information for patients in the UK
- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
  - It was not affecting your ability to drive safely.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

Important information about some of the ingredients of ORAMORPH
This medicine contains
- Ethanol (Alcohol). This product contains 10 volume % ethanol (alcohol). Each dose contains up to 0.81 g of alcohol which is equivalent to 20 ml beer or 8.3 ml wine. This medicine is harmful if you are addicted to alcohol. The amount of alcohol should also be considered if you are pregnant or breast-feeding, have long term (chronic) liver problems or epilepsy, or you are a child

- **Sucrose** This product contains 30 g of sucrose in the 100 ml bottle, 90 g of sucrose in the 300 ml bottle, and 150 g of sucrose in the 500 ml bottle When taken according to the dosage recommendations each dose supplies up to 3 g of sucrose You should not take this product if you have a bowel condition that makes you intolerant to some sugars such as fructose, glucose, galactose or sucrose
- **Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)** - These may cause allergic reactions in some people that could occur some time after taking this medicine The signs may include swelling of the mouth and face, sudden breathing difficulties and your blood pressure being lower than normal

3 HOW TO TAKE ORAMORPH ORAL SOLUTION

Always take this medicine exactly as your doctor has told you
You should check with your doctor or pharmacist if you are not sure

Taking this medicine
- Take this medicine by mouth only
- Use a 5 ml plastic spoon to measure your dose
- They are available from your pharmacist

How much to take
Your doctor will decide the amount of medicine to give you

Adults
- The most that should be taken is 5 to 10 ml (one to two teaspoons) every four hours

Paediatric population

Children 13 to 18 years
- The most that should be taken is 2 5 to 10 ml (half to two teaspoons) every four hours

Children 6 to 12 years
- The most that should be taken is 2 5 to 5 ml (half to one teaspoon) every four hours

Children 1 to 5 years
- The most that should be taken is 2 5 ml (half a teaspoon) every four hours

Children under 1 year
- Do not give this medicine to children under 1 year

Being given more or less of this medicine
- For some people, it may be necessary for the doctor to give a higher dose
- For other people (for example the elderly, people with kidney or liver problems, an underactive adrenal or thyroid gland or prostate problems, and people that should not be sedated) the doctor may decide to use a lower dose

Your body may get used to the medicine (tolerance)
- Do not take more than your doctor has prescribed
- If you have been taking your medicine for some time you may find that it does not seem to be working as well as it did If this happens, talk to your doctor

If you take more ORAMORPH than you should
If you take more of this medicine than you should, talk to a doctor or go to a hospital straight away Take the medicine pack with you This is so the doctor knows what you have taken

If you take more than you should, the following effects may happen
- The black circle in the centre of your eyes (pupil) gets smaller
- You breathe more slowly
- You have low blood pressure

People who have taken an overdose may also get pneumonia from inhaling vomit or foreign matter, symptoms of this may include breathlessness, cough and fever

In more severe cases, very high doses could cause your blood circulation and breathing to slow down and cause unconsciousness for a long time, or even death In children a high dose may cause fits (convulsions)

If you forget to take ORAMORPH
- If you forget a dose, take it as soon as you remember it and take your next dose at the usual time
- If it is nearly time for the next dose, skip the missed dose This is because the time between doses should be at least 4 hours
- Do not take a double dose to make up for a forgotten dose

If you stop taking ORAMORPH
Do not stop treatment with this medicine unless it has been agreed with your doctor Also, it is important you do not stop taking your medicine suddenly This is because your body may have got used to it If you want to stop treatment with ORAMORPH, ask your doctor how to slowly decrease the dose so you avoid withdrawal symptoms Withdrawal symptoms may include body aches, tremors, diarrhoea, stomach pain, feeling sick, flu-like symptoms, fast heartbeat and large pupils Psychological symptoms include an intense feeling of dissatisfaction, anxiety and irritability

4 POSSIBLE SIDE EFFECTS

Like all medicines, ORAMORPH can cause side effects, although not everybody gets them The following side effects may happen with this medicine, their frequency is not known

Allergic reactions
If you have a severe allergic reaction, stop taking this medicine and see a doctor straight away Signs may include swelling of the mouth and face, difficulty breathing, dizziness and skin reactions such as rash and itching

Tell your doctor straight away if you notice the following side effects. You may need urgent medical treatment:
- Having a headache This could be a sign of increased pressure inside your skull
- Feeling dizzy or unsteady when you stand up This could be a sign of a temporary fall in blood pressure (orthostatic hypotension)
- Shallow breathing, with a slow heartbeat (bradycardia) and cold clammy skin
- Feeling restless, irritable or having changes in your mood
- Stomach pain caused by spasm (cramps) of the tubes that carry urine to the bladder or bile to the intestines
- Difficulty breathing (not linked to an allergic reaction)
- Dry mouth or sweating
- Seeing or hearing things that are not there (hallucinations) or feeling confused
- Increased sensitivity to pain
- Dependence on ORAMORPH or withdrawal symptoms (for symptoms see section 3 If you stop taking ORAMORPH) This can happen with any morphine product

Other side effects
- Feeling sick (nausea) or being sick (vomiting)
- Constipation, which can be treated with appropriate laxatives
- Difficulty in passing water (urine)
- Feeling drowsy
- Flushing of your face
- Your heart rate getting faster (tachycardia) or slower (bradycardia) or fast and uneven (palpitations)
- Lower body temperature (hypothermia)
- Lowered sex drive or erection problems
- Muscles feeling tense
- The black circle in the centre of your eyes (pupil) getting smaller (miosis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse This includes any possible side effects not listed in this leaflet You can also report side effects directly (see details below) By reporting side effects you can help provide more information on the safety of this medicine

United Kingdom
Yellow Card Scheme
Website www mhra gov uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel +353 1 6764971
Fax +353 1 6762517
Website www hpra ie
e-mail medsafety@hpra ie

5. HOW TO STORE ORAMORPH ORAL SOLUTION

Keep out of the reach and sight of children

Do not use this medicine after the expiry date which is stated on the bottle label and the outer carton The expiry date refers to the last day of the month

Do not store ORAMORPH above 25°C Store in the original container in order to protect from light

Please return any remaining medicine to your pharmacist 3 months after first opening

Medicines should not be disposed of via wastewater or household waste Ask your pharmacist how to dispose of medicines no longer required These measures will help to protect the environment

6 FURTHER INFORMATION

What ORAMORPH contains
- Each 5 ml contains 10 mg of morphine sulfate as the active ingredient
- The other ingredients are alcohol (ethanol), corn syrup, sucrose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and purified water

What ORAMORPH looks like and content of the pack
ORAMORPH is a solution and is available in bottles of 100, 250, 300 and 500 ml The bottles come in cartons

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation for ORAMORPH is held by

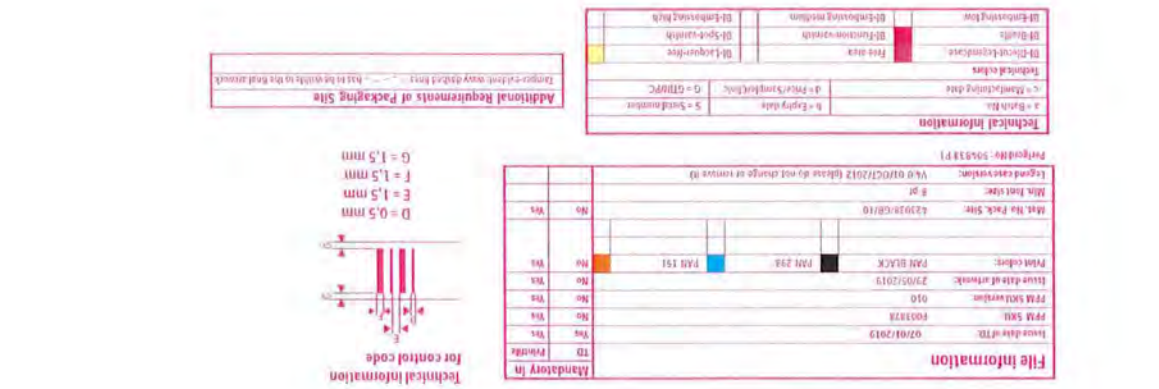
Boehringer Ingelheim International GmbH,
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

and the solution is manufactured by

Istituto de Angeli S r l at
Località Prulli Si Sotto n 103/C, 50066 Reggello (FI), Italy

This leaflet was revised in March 2019

Ref 3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Mandatory In
Additional Requirements of Packaging Site
Technical Information for control code
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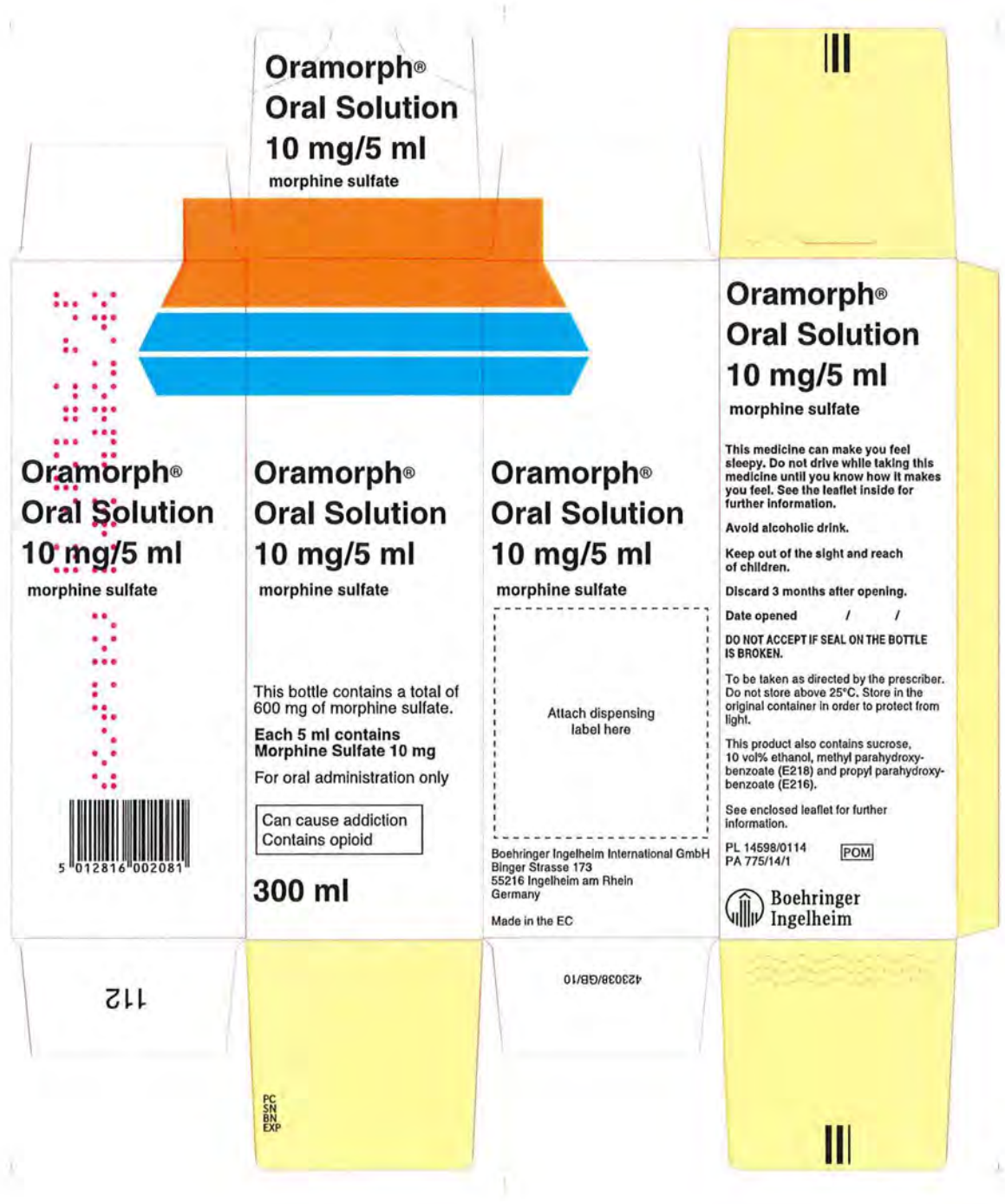
E = 1,5 mm
F = 1,5 mm
G = 1,5 mm


Oramorph®
Oral Solution
10 mg/5 ml
morphine sulfate
This bottle contains a total of 600 mg of morphine sulfate.
Each 5 ml contains Morphine Sulfate 10 mg
For oral administration only
Can cause addiction
Contains opioid
300 ml
Attach dispensing label here
Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany
Made in the EC
This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for further information.
Avoid alcoholic drink.
Keep out of the sight and reach of children.
Discard 3 months after opening.
Date opened / /
DO NOT ACCEPT IF SEAL ON THE BOTTLE IS BROKEN.
To be taken as directed by the prescriber. Do not store above 25°C. Store in the original container in order to protect from light.
This product also contains sucrose, 10 vol% ethanol, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).
See enclosed leaflet for further information.
PL 14598/0114
PA 775/14/1
POM
Boehringer Ingelheim
5 012816 002081
112
PC
SN
BN
EXP
423038/GB/10

Ref 4

Oramorph® Oral Solution 10 mg/5 ml

morphine sulfate

This bottle contains a total of 600 mg of morphine sulfate.

Each 5 ml contains
Morphine Sulfate 10 mg

Can cause addiction
Contains opioid

300 ml

430256/GB/8

For oral administration only. This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for further information. Avoid alcoholic drink.

Keep out of the sight and reach of children.

DO NOT ACCEPT IF SEAL ON THE BOTTLE IS BROKEN.

To be taken as directed by the prescriber. Do not store above 25°C. Store in the original container in order to protect from light.

This product also contains sucrose, 10 vol% ethanol, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

See enclosed leaflet for further information.

Boehringer Ingelheim
International GmbH, 55216
Ingelheim am Rhein, Germany.

Discard 3 months after opening.
Date opened / /

PL 14598/0114
PA 775/14/1

POM

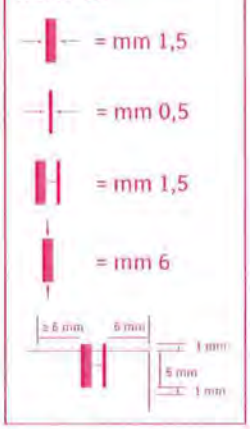
BN
EXP

File information		Mandatory in	
		TD	Printfile
Issue date of TD:	08/01/2019	Yes	Yes
PPM SKU:	P003877	No	Yes
PPM SKU version:	008	No	Yes
Issue date of artwork:	29/05/2019	No	Yes
Print colors:	PAN BLACK / PAN 298 / PAN 151	No	Yes
Mat. No. Pack. Site:	430256/GB/8	No	Yes
Min. font size:	8 pt		
Legend case version:	V4.0 01/OCT/2012 (please do not change or remove it)		

Perigord No: 504832 P1

Technical information				
a = Batch No.		b = Expiry date		
c = Manufacturing date		d = Price/Sample/Cinic		
Technical colors				
BI-Diecut-Legendcase		Free area		BI-Lacquer-free
BI-Braille		BI-Function-varnish		BI-Spot-varnish

Technical information control code



Ref 5

Package Leaflet: Information for the User

Oramorph® Oral Solution 10 mg/5 ml

(morphine sulfate)

Boehringer Ingelheim

437137/GB/18

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORAMORPH ORAL SOLUTION IS AND WHAT IT IS USED FOR

The name of your medicine is ORAMORPH Oral Solution 10 mg/5 ml (called ORAMORPH in this leaflet).
- It contains a medicine called morphine sulfate. This belongs to a group of medicines called 'opioid analgesics'
- It is used to relieve severe pain

2. BEFORE YOU TAKE ORAMORPH ORAL SOLUTION

Do not take ORAMORPH if:
- You are allergic (hypersensitive) to morphine sulfate or any of the other ingredients of ORAMORPH (listed in Section 6 below)
- You have problems with your lungs or breathing such as 'hypoventilation' or 'Chronic Obstructive Pulmonary Disease' (COPD)
- You are having an asthma attack
- You have sudden or recent liver problems
- You have recently had a head injury
- You have something called 'phaeochromocytoma'. This is a rare tumour which is not malignant
- You have fits (convulsions) or increased pressure inside your skull
- The person taking the medicine is in a deep and prolonged unconscious state (coma)
- You are addicted to alcohol or have recently consumed large amounts of alcohol
- You are taking or have in the last two weeks taken medication to treat depression such as monoamine-oxidase inhibitors (MAOIs)
- You have paralytic ileus (loss of intestinal movement)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Take special care with ORAMORPH
Check with your doctor or pharmacist before taking your medicine if:
- You are pregnant, trying to become pregnant or if you are breast-feeding
- You have had an operation within the last 24 hours
- You have a particular lung problem that causes shortness of breath called emphysema or you have heart failure
- You have shock (circulatory failure)
- You have asthma
- You have gall bladder problems
- You have long term (chronic) liver or kidney problems
- You are a man who has prostate problems
- You have an under-active thyroid gland or swelling of your skin (myxoedema)
- Your spine is unusually curved (kyphoscoliosis)
- You have bowel problems
- You have an under-active adrenal gland (adrenocortical insufficiency)
- You are very overweight

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking ORAMORPH.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because ORAMORPH can affect the way some other medicines work. Also some other medicines can affect the way ORAMORPH works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- Medicines to help you sleep, make you feel less anxious or calm you down such as tranquilisers, hypnotics, sedatives, antipsychotics or tricyclic antidepressants
- Anaesthetics - used during operations
- Domperidone, metoclopramide or phenothiazine - medicines for feeling sick (nausea) and being sick (vomiting)
- Mexiletine and esmolol - for controlling heart rhythm
- Ritonavir - for HIV infections
- Cimetidine - for stomach ulcers, indigestion or heartburn
- Monoamine oxidase inhibitors (MAOIs) - for depression
- Rifampicin - used to treat tuberculosis and other infections
- Gabapentin - for epilepsy and long lasting pain caused by damage to the nerves

Taking ORAMORPH with food and drink
You should avoid alcohol whilst taking this medicine.

Pregnancy and breast-feeding
Talk to your doctor before taking this medicine if you are pregnant, trying to become pregnant or if you are breast-feeding. If you take this medicine during pregnancy or while breast-feeding, it may slow down the baby's breathing. If you take this medicine for a long time whilst pregnant, it may mean that the baby will be born showing signs of withdrawal.

Operations and anaesthetics
Tell your doctor or pharmacist if you are due to have an operation or an anaesthetic or if you have had an operation or an anaesthetic within the last 24 hours.

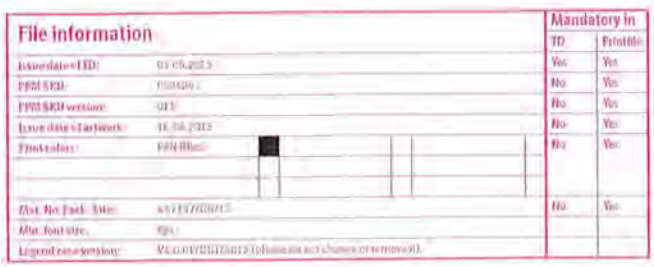
Driving and using machines
You may feel drowsy while taking this medicine. If this happens, do not drive or use any tools or machines.

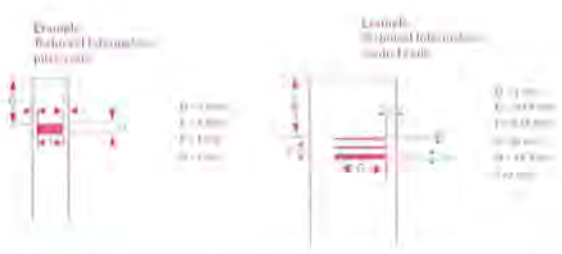
Additional information for patients in the UK:
- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
  - It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

Important information about some of the ingredients of ORAMORPH
This medicine contains:

- **Ethanol (Alcohol):** This product contains 10 volume % ethanol (alcohol). Each dose contains up to 0.81 g of alcohol which is equivalent to 20 ml beer or 8.3 ml wine. This medicine is harmful if you are addicted to alcohol. The amount of alcohol should also be considered if you are pregnant or breast-feeding, have long term (chronic) liver problems or epilepsy, or you are a child
- **Sucrose:** This product contains 30 g of sucrose in the 100 ml bottle, 90 g of sucrose in the 300 ml bottle, and 150 g of sucrose in the 500 ml bottle. When taken according to the dosage recommendations each dose supplies up to 3 g of sucrose. You should not take this product if you have a bowel condition that makes you intolerant to some sugars such as fructose, glucose, galactose or sucrose
- **Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) -** These may cause allergic reactions in some people that could occur some time after taking this medicine. The signs may include swelling of the mouth and face, sudden breathing difficulties and your blood pressure being lower than normal





3 HOW TO TAKE ORAMORPH ORAL SOLUTION

Always take this medicine exactly as your doctor has told you
You should check with your doctor or pharmacist if you are not sure

Taking this medicine
- Take this medicine by mouth only
- Use a 5 ml plastic spoon to measure your dose
- They are available from your pharmacist

How much to take
Your doctor will decide the amount of medicine to give you

Adults
The most that should be taken is 5 to 10 ml (one to two teaspoons) every four hours

Paediatric population

Children 13 to 18 years
- The most that should be taken is 2 5 to 10 ml (half to two teaspoons) every four hours

Children 6 to 12 years
- The most that should be taken is 2 5 to 5 ml (half to one teaspoon) every four hours

Children 1 to 5 years
- The most that should be taken is 2 5 ml (half a teaspoon) every four hours

Children under 1 year
Do not give this medicine to children under 1 year

Being given more or less of this medicine
- For some people, it may be necessary for the doctor to give a higher dose
- For other people (for example the elderly, people with kidney or liver problems, an underactive adrenal or thyroid gland or prostate problems, and people that should not be sedated) the doctor may decide to use a lower dose

Your body may get used to the medicine (tolerance)
- Do not take more than your doctor has prescribed
- If you have been taking your medicine for some time you may find that it does not seem to be working as well as it did If this happens, talk to your doctor

If you take more ORAMORPH than you should
If you take more of this medicine than you should, talk to a doctor or go to a hospital straight away Take the medicine pack with you This is so the doctor knows what you have taken

If you take more than you should, the following effects may happen
The black circle in the centre of your eyes (pupil) gets smaller
- You breathe more slowly
- You have low blood pressure

In more severe cases, very high doses could cause your blood circulation to slow down and cause unconsciousness for a long time, or even death In children a high dose may cause fits (convulsions)

If you forget to take ORAMORPH
If you forget a dose, take it as soon as you remember it and take your next dose at the usual time
If it is nearly time for the next dose, skip the missed dose This is because the time between doses should be at least 4 hours
- Do not take a double dose to make up for a forgotten dose

If you stop taking ORAMORPH
It is important to talk to your doctor if you want to stop taking your medicine Do not stop taking your medicine suddenly This is because your body may have got used to it Also, you may need to have your dose lowered slowly

4 POSSIBLE SIDE EFFECTS

Like all medicines, ORAMORPH can cause side effects, although not everybody gets them The following side effects may happen with this medicine

Allergic reactions
If you have a severe allergic reaction, stop taking this medicine and see a doctor straight away Signs may include swelling of the mouth and face, difficulty breathing, dizziness and skin reactions such as rash and itching

Tell your doctor straight away if you notice the following side effects
You may need urgent medical treatment
- Having a headache This could be a sign of increased pressure inside your skull
- Feeling dizzy or unsteady when you stand up This could be a sign of a temporary fall in blood pressure (orthostatic hypotension)
- Shallow breathing, with a slow heartbeat (bradycardia) and cold clammy skin
  Feeling restless, irritable or having changes in your mood
- Stomach pain caused by spasm (cramps) of the tubes that carry urine to the bladder or bile to the intestines
- Difficulty breathing (not linked to an allergic reaction)

Other side effects
- Feeling sick (nausea) or being sick (vomiting)
  Constipation, which can be treated with appropriate laxatives
- Difficulty in passing water (urine)
- Feeling drowsy
- Dry mouth, sweating and flushing of your face
  Your heart rate getting faster (tachycardia) or slower (bradycardia) or fast and uneven (palpitations)
- Lower body temperature (hypothermia)
- Lowered sex drive or erection problems
- Seeing or hearing things that are not there (hallucinations) or feeling confused
  Muscles feeling tense
- The black circle in the centre of your eyes (pupil) getting smaller (miosis)
  Dependence on ORAMORPH This can happen with any morphine product

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse This includes any possible side effects not listed in this leaflet You can also report side effects directly (see details below) By reporting side effects you can help provide more information on the safety of this medicine

United Kingdom
Yellow Card Scheme
Website www mhra gov uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel +353 1 6764971
Fax +353 1 6762517
Website www hpra ie
e-mail medsafety@hpra ie

5 HOW TO STORE ORAMORPH ORAL SOLUTION

Keep out of the reach and sight of children

Do not use this medicine after the expiry date which is stated on the bottle label and the outer carton The expiry date refers to the last day of the month

Do not store ORAMORPH above 25°C Store in the original container in order to protect from light

Please return any remaining medicine to your pharmacist 3 months after first opening

Medicines should not be disposed of via wastewater or household waste Ask your pharmacist how to dispose of medicines no longer required These measures will help to protect the environment

6 FURTHER INFORMATION

What ORAMORPH contains
- Each 5 ml contains 10 mg of morphine sulfate as the active ingredient
- The other ingredients are alcohol (ethanol), corn syrup, sucrose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and purified water

What ORAMORPH looks like and content of the pack
ORAMORPH is a solution and is available in bottles of 100, 250, 300 and 500 ml The bottles come in cartons

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation for ORAMORPH is held by

Boehringer Ingelheim Limited, Ellesfield Avenue,
Bracknell, Berkshire, RG12 8YS, United Kingdom

and the solution is manufactured by

Istituto de Angeli S r l at
Localita Prulli Si Sotto n 103/C, 50066 Reggello (FI), Italy

This leaflet was revised in June 2015

Ref 6.

Package Leaflet: Information for the User

437737/GB/15

Oramorph® Oral Solution 10 mg/5 ml

(morphine sulfate)

Boehringer Ingelheim

1

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ORAMORPH ORAL SOLUTION IS AND WHAT IT IS USED FOR

The name of your medicine is ORAMORPH Oral Solution 10 mg/5 ml (called ORAMORPH in this leaflet).
- It contains a medicine called morphine sulfate. This belongs to a group of medicines called 'opioid analgesics'
- It is used to relieve severe pain

2. BEFORE YOU TAKE ORAMORPH ORAL SOLUTION

Do not take ORAMORPH if:
- You are allergic (hypersensitive) to morphine sulfate or any of the other ingredients of ORAMORPH (listed in Section 6 below)
- You have problems with your lungs or breathing such as 'hypoventilation' or 'Chronic Obstructive Pulmonary Disease' (COPD)
- You are having an asthma attack
- You have sudden or recent liver problems
- You have recently had a head injury
- You have something called 'phaeochromocytoma'. This is a rare tumour which is not malignant
- You have fits (convulsions) or increased pressure inside your skull
- The person taking the medicine is in a deep and prolonged unconscious state (coma)
- You are addicted to alcohol or have recently consumed large amounts of alcohol
- You are taking or have in the last two weeks taken medication to treat depression such as monoamine-oxidase inhibitors (MAOIs)
- You have paralytic ileus (loss of intestinal movement)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Take special care with ORAMORPH
Check with your doctor or pharmacist before taking your medicine if:
- You are pregnant, trying to become pregnant or if you are breast-feeding
- You have had an operation within the last 24 hours
- You have a particular lung problem that causes shortness of breath called emphysema or you have heart failure
- You have shock (circulatory failure)
- You have asthma
- You have gall bladder problems
- You have long term (chronic) liver or kidney problems
- You are a man who has prostate problems
- You have an under-active thyroid gland or swelling of your skin (myxoedema)
- Your spine is unusually curved (kyphoscoliosis)
- You have bowel problems
- You have an under-active adrenal gland (adrenocortical insufficiency)
- You are very overweight

4

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking ORAMORPH.

5

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because ORAMORPH can affect the way some other medicines work. Also some other medicines can affect the way ORAMORPH works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- Medicines to help you sleep, make you feel less anxious or calm you down such as tranquillisers, hypnotics, sedatives, antipsychotics or tricyclic antidepressants
- Anaesthetics - used during operations 2
- Domperidone, metoclopramide or phenothiazine - medicines for feeling sick (nausea) and being sick (vomiting)
- Mexiletine and esmolol - for controlling heart rhythm
- Ritonavir - for HIV infections
- Cimetidine - for stomach ulcers, indigestion or heartburn
- Monoamine oxidase inhibitors (MAOIs) - for depression
- Rifampicin - used to treat tuberculosis and other infections
- Gabapentin - for epilepsy and long lasting pain caused by damage to the nerves

Taking ORAMORPH with food and drink
You should avoid alcohol whilst taking this medicine.

Pregnancy and breast-feeding
Talk to your doctor before taking this medicine if you are pregnant, trying to become pregnant or if you are breast-feeding. If you take this medicine during pregnancy or while breast-feeding, it may slow down the baby's breathing. If you take this medicine for a long time whilst pregnant, it may mean that the baby will be born showing signs of withdrawal. 3

Operations and anaesthetics
Tell your doctor or pharmacist if you are due to have an operation or an anaesthetic or if you have had an operation or an anaesthetic within the last 24 hours.

Driving and using machines
You may feel drowsy while taking this medicine. If this happens, do not drive or use any tools or machines.

Additional information for patients in the UK:
- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
  - It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

Important information about some of the ingredients of ORAMORPH
This medicine contains:

- **Ethanol (Alcohol):** This product contains 10 volume % ethanol (alcohol). Each dose contains up to 0.81 g of alcohol which is equivalent to 20 ml beer or 8.3 ml wine. This medicine is harmful if you are addicted to alcohol. The amount of alcohol should also be considered if you are pregnant or breast-feeding, have long term (chronic) liver problems or epilepsy, or you are a child
- **Sucrose:** This product contains 30 g of sucrose in the 100 ml bottle, 90 g of sucrose in the 300 ml bottle, and 150 g of sucrose in the 500 ml bottle. When taken according to the dosage recommendations each dose supplies up to 3 g of sucrose. You should not take this product if you have a bowel condition that makes you intolerant to some sugars such as fructose, glucose, galactose or sucrose
- **Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)** - These may cause allergic reactions in some people that could occur some time after taking this medicine. The signs may include swelling of the mouth and face, sudden breathing difficulties and your blood pressure being lower than normal

File information

		Mandatory in ID	Mandatory in Frontside
Issue date of ID:	[illegible]	Yes	Yes
PPM SKU:	[illegible]	No	Yes
PPM SKU version:	015	No	Yes
Issue date of artwork:	15.06.2015	No	Yes
Print colors:	[illegible]	No	Yes
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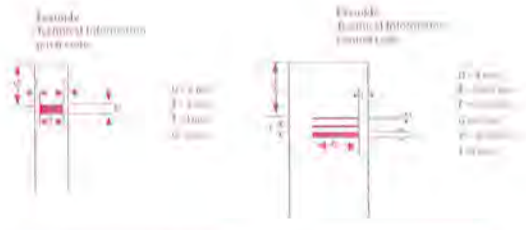
Min. font size:	[illegible]		
Legend case version:	[illegible]		

Technical information



Additional Requirements of Packaging Site:

Summary of Comments on uk-mockup-pl-trackchange_2.pdf

Page: 1

Number: 1 Author: Subject: Sticky Note Date: 18/09/2019 17:09:24

heading amended to 'Other medicines and ORAMORPH'

Number: 2 Author: Subject: Sticky Note Date: 07/09/2018 16:00:50

Insert:

- Taking ORAMORPH together with sedative medicines such as benzodiazepines or related medicines increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, taking ORAMORPH together with these types of medicines should only be considered when other treatment options are not possible. However if your doctor does prescribe ORAMORPH together with sedative medicines the dose and duration of taking the treatments together should be limited by your doctor.
- Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor if you experience these symptoms

Number: 3 Author: Subject: Sticky Note Date: 07/09/2018 16:01:19

Add: which should be treated by a doctor.

Number: 4 Author: Subject: Sticky Note Date: 07/09/2018 15:59:39

Insert: You have once been dependent on drugs or alcohol

Number: 5 Author: Subject: Sticky Note Date: 07/09/2018 16:00:14

Insert:

Warnings and precautions

Talk to your doctor, nurse or pharmacist if you experience any of the following symptoms while you are taking ORAMORPH

- Increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in strong analgesic ("painkiller")
- Weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of your adrenal glands producing too little of a hormone called cortisol, and you may need to take a hormone supplement
- Loss of libido (sex drive), difficulty getting an erection, menstrual periods stopping. This may be because of your body producing less sex hormones
- You feel that you are becoming dependent on ORAMORPH while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for the pain. This is particularly important to look out for if you have once been dependent on drugs or alcohol
- Withdrawal symptoms. The most common withdrawal symptoms are mentioned in section 3. If this occurs, your doctor may change the type of medicine or the times between doses

3. HOW TO TAKE ORAMORPH ORAL SOLUTION

Always take this medicine exactly as your doctor has told you.
You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Take this medicine by mouth only
- Use a 5 ml plastic spoon to measure your dose
- They are available from your pharmacist

How much to take
Your doctor will decide the amount of medicine to give you.

Adults
- The most that should be taken is 5 to 10 ml (one to two teaspoons) every four hours

Paediatric population

Children 13 to 18 years
- The most that should be taken is 2.5 to 10 ml (half to two teaspoons) every four hours

Children 6 to 12 years
- The most that should be taken is 2.5 to 5 ml (half to one teaspoon) every four hours

Children 1 to 5 years
- The most that should be taken is 2.5 ml (half a teaspoon) every four hours

Children under 1 year
- Do not give this medicine to children under 1 year

Being given more or less of this medicine
- For some people, it may be necessary for the doctor to give a higher dose
- For other people (for example the elderly, people with kidney or liver problems, an underactive adrenal or thyroid gland or prostate problems, and people that should not be sedated) the doctor may decide to use a lower dose

Your body may get used to the medicine (tolerance)
- Do not take more than your doctor has prescribed
- If you have been taking your medicine for some time you may find that it does not seem to be working as well as it did. If this happens, talk to your doctor

If you take more ORAMORPH than you should
If you take more of this medicine than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you take more than you should, the following effects may happen:
- The black circle in the centre of your eyes (pupil) gets smaller
- You breathe more slowly
- You have low blood pressure

In more severe cases, very high doses could cause your blood circulation to slow down and cause unconsciousness for a long time, or even death. In children a high dose may cause fits (convulsions).

If you forget to take ORAMORPH
- If you forget a dose, take it as soon as you remember it and take your next dose at the usual time
- If it is nearly time for the next dose, skip the missed dose. This is because the time between doses should be at least 4 hours
- Do not take a double dose to make up for a forgotten dose

If you stop taking ORAMORPH
It is important to talk to your doctor if you want to stop taking your medicine. Do not stop taking your medicine suddenly. This is because your body may have got used to it. Also, you may need to have your dose lowered slowly.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ORAMORPH can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Allergic reactions
If you have a severe allergic reaction, stop taking this medicine and see a doctor straight away. Signs may include swelling of the mouth and face, difficulty breathing, dizziness and skin reactions such as rash and itching.

Tell your doctor straight away if you notice the following side effects. You may need urgent medical treatment:
- Having a headache. This could be a sign of increased pressure inside your skull
- Feeling dizzy or unsteady when you stand up. This could be a sign of a temporary fall in blood pressure (orthostatic hypotension)
- Shallow breathing, with a slow heartbeat (bradycardia) and cold clammy skin
- Feeling restless, irritable or having changes in your mood
- Stomach pain caused by spasm (cramps) of the tubes that carry urine to the bladder or bile to the intestines
- Difficulty breathing (not linked to an allergic reaction)

Other side effects
- Feeling sick (nausea) or being sick (vomiting)
- Constipation, which can be treated with appropriate laxatives
- Difficulty in passing water (urine)
- Feeling drowsy
- Dry mouth, sweating and flushing of your face
- Your heart rate getting faster (tachycardia) or slower (bradycardia) or fast and uneven (palpitations)
- Lower body temperature (hypothermia)
- Lowered sex drive or erection problems
- Seeing or hearing things that are not there (hallucinations) or feeling confused
- Muscles feeling tense
- The black circle in the centre of your eyes (pupil) getting smaller (miosis)
- Dependence on ORAMORPH. This can happen with any morphine product

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

5. HOW TO STORE ORAMORPH ORAL SOLUTION

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the bottle label and the outer carton. The expiry date refers to the last day of the month.

Do not store ORAMORPH above 25°C. Store in the original container in order to protect from light.

Please return any remaining medicine to your pharmacist 3 months after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ORAMORPH contains
- Each 5 ml contains 10 mg of morphine sulfate as the active ingredient
- The other ingredients are alcohol (ethanol), corn syrup, sucrose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and purified water

What ORAMORPH looks like and content of the pack
ORAMORPH is a solution and is available in bottles of 100, 250, 300 and 500 ml. The bottles come in cartons.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation for ORAMORPH is held by:

Boehringer Ingelheim Limited, Ellesfield Avenue,
Bracknell, Berkshire, RG12 8YS, United Kingdom

and the solution is manufactured by:

Istituto de Angeli S.r.l. at:
Località Prulli SI Sotto n. 103/C, 50066 Reggello (FI), Italy

This leaflet was revised in June 2015.

Number 1 Author Subject Sticky Note Date 18/09/2019 17 21 53
Insert after ORAMORPH or withdrawal symptoms (for symptoms see section3 If you stop taking ORAMORPH)

In addition this wording was moved to section above after Increased sensitivity to pain,

Number 2 Author Subject Sticky Note Date 07/09/2018 16 12 04
add or search for MHRA Yellow Card in the Google Play or Apple App store

Number 3 Author Subject Sticky Note Date 07/09/2018 16 02 54
Insert at start People who have taken an overdose may also get pneumonia from inhaling vomit or foreign matter, symptoms of this may include breathlessness, cough and fever

Number 4 Author Subject Sticky Note Date 07/09/2018 16 03 25
Insert 'and breathing' after 'circulation'

Number 5 Author Subject Sticky Note Date 07/09/2018 16 07 56
Reword to Do not stop treatment with this medicine unless it has been agreed with your doctor Also, it is important you do not stop taking your medicine suddenly This is because your body may have got used to it If you want to stop treatment with ORAMORPH, ask your doctor how to slowly decrease the dose so you avoid withdrawal symptoms Withdrawal symptoms may include body aches, tremors, diarrhoea stomach pain, feeling sick, flu-like symptoms, fast heartbeat and large pupils/ Psychological symptoms include an intense feeling of dissatisfaction, anxiety and irritability

Number 6 Author Subject Sticky Note Date 07/09/2018 16 08 33
Add their frequency is not known

Number 7 Author Subject Sticky Note Date 18/09/2019 17 12 51
Marketing Authorisation Holder amended to Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

Number 8 Author Subject Sticky Note Date 07/09/2018 16 12 30
replace with September 2018

Number 9 Author Subject Sticky Note Date 07/09/2018 16 13 03
replace with 2018

Number 10 Author Subject Sticky Note Date 18/09/2019 17 20 49
The following side effects removed from under 'Other side effects' into this section
-Dry mouth or sweating
-Seeing or hearing things that are not there (hallucinations) or feeling confused

The following side effect was added
-Increased sensitivity to pain

Number 11 Author Subject Sticky Note Date 07/09/2018 16 12 46
update number