Public Assessment Report

Decentralised Procedure

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion

(oxycodone hydrochloride)

UK/H/2915/001/DC
UK licence numbers: PL 29831/0359

Wockhardt UK Limited
LAY SUMMARY

On 7th May 2010, the MHRA granted Wockhardt UK Limited a Marketing Authorisation (licence) for the medicinal product Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion (PL 29831/0359, UK/H/2915/001/DC). This is a prescription-only medicine (POM) intended for use in adults only.

Oxycodone belongs to a group of medicines known as opioid analgesics, which are strong painkillers. Oxycodone injection is used in the treatment of pain requiring the use of a strong painkiller, as follows:

- Moderate to severe pain in patients with cancer
- Pain following an operation

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

## Information About Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion</th>
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<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
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<tr>
<td>Active Substance</td>
<td>Oxycodone hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Solution for injection or infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>10mg / ml</td>
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</table>
| MA Holder | Wockhardt UK Ltd  
> Ash Road North  
> Wrexham  
> LL13 9UF  
> UK |
| RMS | UK |
| CMS | CY, IE, MT, PL |
| Procedure Number | UK/H/2915/001/DC |
| Timetable | Day 210 (end of procedure) – 21st April 2010 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains oxycodone hydrochloride 10 mg (equivalent to 9 mg of oxycodone base).
Each 1 ml ampoule contains oxycodone hydrochloride 10 mg (equivalent to 9 mg of oxycodone base).
Each 2 ml contains oxycodone hydrochloride 20 mg (equivalent to 18 mg of oxycodone base).
This medicinal product contains less than 1 mmol sodium (23 mg) per dose.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection or infusion (injection or infusion).
A Clear, colourless solution practically free of particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

4.2 Posology and method of administration
Route of administration:
Subcutaneous injection or infusion.
Intravenous injection or infusion.

Posology:
The dose should be adjusted according to the severity of pain, the total condition of the patient and previous or concurrent medication.

Adults over 18 years:
The following starting doses are recommended. A gradual increase in dose may be required if analgesia is inadequate or if pain severity increases.

i.v. (Bolus): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over one to two minutes.

Doses should not be administered more frequently than every four hours.

i.v. (Infusion): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. A starting dose of 2 mg/hour is recommended.

i.v. (PCA): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Bolus doses of 0.03 mg/kg should be administered with a minimum lock-out time of five minutes.

s.c. (Bolus): Use as 10 mg/ml concentration. A starting dose of 5 mg is recommended, repeated at four-hourly intervals as required.
s.c. (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections if required. A starting dose of 7.5 mg/day is recommended in opioid naïve patients, titrating gradually according to symptom control. Cancer patients transferring from oral oxycodone may require much higher doses (see below).

**Transferring patients between oral and parenteral oxycodone:**
The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

**Elderly:**
Elderly patients should be treated with caution. The lowest dose should be administered with careful titration to pain control.

**Patients with renal and hepatic impairment:**
Patients with mild to moderate renal impairment and/or mild hepatic impairment should be treated with caution. The lowest dose should be given with careful titration to pain control.

**Children under 18 years:**
There are no data on the use of Oxycodone injection in patients under 18 years of age.

**Use in non-malignant pain:**
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

**Cessation of therapy:**
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

### 4.3 Contraindications
Oxycodone injection is contraindicated in patients with known hypersensitivity to oxycodone or any of the other constituents, or in any situation where opioids are contraindicated; respiratory depression; head injury; paralytic ileus; acute abdomen; chronic obstructive airways disease; cor pulmonale; chronic bronchial asthma; hypercarbia; moderate to severe hepatic impairment; severe renal impairment (creatinine clearance <10 ml/min); chronic constipation; concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use; pregnancy; lactation.

### 4.4 Special warnings and precautions for use
The major risk of opioid excess is respiratory depression. As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychoses, diseases of the biliary tract, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, pancreatitis, chronic renal and hepatic disease or severe pulmonary disease and debilitated, elderly and infirm patients. Oxycodone injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxycodone injection should be discontinued immediately.

The patient may develop tolerance to oxycodone with chronic use and require progressively higher doses to maintain pain control. The patient may develop physical dependence, in which case an abstinence syndrome may be seen following abrupt cessation.

For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history. Oxycodone injection should be used with particular care in patients with a history of alcohol and drug abuse.
If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate pain relief with a minimum of side effects. There must be frequent contact between physician and patient so that dosage adjustments can be made. It is strongly recommended that the physician defines treatment outcomes in accordance with pain management guidelines. The physician and patient can then agree to discontinue treatment if these objectives are not met.

Oxycodone has an abuse liability similar to other strong opioids and should be used with caution in opioid-dependent patients. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

Oxycodone injection contains approximately 5mg sodium per ml i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

There is an enhanced CNS depressant effect with drugs such as tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis.

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. While these pathways may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.

4.6 Pregnancy and lactation

Pregnancy

The effect of oxycodone in human reproduction has not been adequately studied. No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult dose of 160 mg/day, respectively, did not reveal evidence of harm to the foetus due to oxycodone. Oxycodone injection is not recommended for use in pregnancy nor during labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Lactation

Oxycodone is secreted in breast milk and may cause harmful effects in the newborn (respiratory depression, somnolence, lethargy). Oxycodone is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. Therefore patients should not drive or operate machinery, if affected.

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Tolerance and Dependence, below). Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.

The adverse drug reactions seen whilst being treated with oxycodone were:

**Endocrine disorders:**

Uncommon (>1/1,000, <1/100): syndrome of inappropriate antidiuretic hormone secretion.

**Metabolism and nutrition disorders:**

Common (>1/100, <1/10): anorexia

Uncommon (>1/1,000, <1/100): dehydration, weight change, peripheral oedema, oedema, thirst.
Psychiatric disorders (see tolerance and dependence below):
Common (>1/100, <1/10): abnormal dreams, anxiety, confusion, insomnia, nervousness, abnormal thinking.
Uncommon (>1/1,000, <1/100): libido decreased, depression, hallucinations, depersonalisation, euphoria, mood changes, agitation, emotional lability.

Nervous system disorders:
Very common (>1/10): somnolence, dizziness.
Common (>1/100, <1/10): faintness, asthenia, headache.
Uncommon (>1/1,000, <1/100): abnormal gait, amnesia, hyperkinesia, hypertonia, hypoesthesia, hypotonia, speech disorder, stupor, tremor, twitching, vertigo, epileptic seizures, paraesthesia, withdrawal syndrome, malaise, muscle contractions involuntary.

Eye disorders:
Uncommon (>1/1,000, <1/100): lacrimation disorder, miosis, abnormal vision.

Ear and labyrinth disorders:
Uncommon (>1/1,000, <1/100): tinnitus.

Cardiac disorders:
Common (>1/100, <1/10): Orthostatic hypotension.
Uncommon (>1/1,000, <1/100): palpitations (in the context of withdrawal syndrome), hypotension, syncope.

Vascular disorders:
Uncommon (>1/1,000, < 1/100): vasodilation.

Respiratory, thoracic and mediastinal disorders:
Common (>1/100, <1/10): dyspnoea, bronchospasm.
Uncommon >1/1,000, <1/100): rhinitis, epistaxis, hiccup, voice alteration, respiratory depression.

Gastrointestinal disorders:
Very common (>1/10): constipation, nausea, vomiting.
Common (>1/100, <1/10): abdominal pain, anorexia, diarrhoea, dry mouth, dyspepsia,
Uncommon (>1/1,000, <1/100): dysphagia, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis, biliary spasm, gastrointestinal disorders, taste perversion.

Skin and subcutaneous tissue disorders:
Very common (>1/10): pruritus.
Common (>1/100, <1/10): rash, sweating.
Uncommon (>1/1,000, <1/100): dry skin, urticaria.

Renal and urinary disorders:
Common (>1/100, <1/10): urinary disorders.
Uncommon (>1/1,000, <1/100): urinary retention, ureteral spasm.
Reproductive system and breast disorders:
Uncommon (>1/1,000, <1/100): impotence, amenorrhoea.

General disorders and administration site conditions:
Common (>1/100, <1/10): fever, chills.
Uncommon >1/1,000, <1/100): chest pain, allergic reaction, anaphylactic reaction, anaphylactoid reaction, drug dependence.

Tolerance and Dependence:
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of Oxycodone injection may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnina, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

The development of psychological dependence (addiction) to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of psychological dependence (addiction) in chronic pain patients.

Oxycodone injection should be used with particular care in patients with a history of alcohol and drug abuse.

4.9 Overdose

Symptoms of overdosage
Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression, hypotension and hallucinations. Nausea and vomiting are common in less severe cases. Non-cardiac pulmonary oedema and rhabdomyolysis are particularly common after intravenous injection of opioid analgesics. Circulatory failure and somnolence progressing to stupor or coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic drugs.

Treatment of overdosage
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2mg for an adult and 0.01mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state.

Intramuscular naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

The patient should be observed for at least 6 hours after the last dose of naloxone.
Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

5  PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opioid receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative.

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from Oxycodone injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours.

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphone and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant.

The active drug and its metabolites are excreted in both urine and faeces.

The plasma concentrations of oxycodone are only minimally affected by age, being 15% greater in elderly as compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

The drug penetrates the placenta and can be found in breast milk.

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

When compared to normal subjects, patients with mild to severe renal dysfunction may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

5.3 Preclinical safety data

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 μg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 μg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/ml or greater with metabolic activation.
and at 400 μg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Citric acid monohydrate
- Sodium citrate
- Sodium chloride
- Hydrochloric acid (for pH adjustment)
- Sodium hydroxide (for pH adjustment)
- Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Cyclizine at concentrations of 3 mg/ml or less, when mixed with Oxycodone injection, either undiluted or diluted with water for injections, shows no sign of precipitation over a period of 24 hours storage at room temperature. Precipitation has been shown to occur in mixtures with Oxycodone injection at cyclizine concentrations greater than 3 mg/ml or when diluted with 0.9% saline. It is recommended that water for injections be used as a diluent when cyclizine and oxycodone hydrochloride are co-administered either intravenously or subcutaneously as an infusion.

Prochlorperazine is chemically incompatible with Oxycodone injection.

6.3 Shelf life
Unopened: 2 years.

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution, dilution, etc as taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Type I clear glass ampoules: 1 ml and 2 ml.

Pack size: 5 ampoules.

6.6 Special precautions for disposal
Oxycodone injection has been shown to be compatible with the following drugs:

- Hyoscine butylbromide
- Hyoscine hydrobromide
- Dexamethasone sodium phosphate
- Haloperidol
- Midazolam hydrochloride
- Metoclopramide hydrochloride
- Levomepromazine hydrochloride
Oxycodone injection, undiluted or diluted to 1 mg/ml with 0.9% w/v saline, 5% w/v dextrose or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags, over a 24 hour period at room temperature.

The injection, whether undiluted or diluted to 1 mg/ml in the infusion fluids used in these studies and contained in the various assemblies, does not need to be protected from light.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0359

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/05/2010

10 DATE OF REVISION OF THE TEXT
07/05/2010
Module 3

Product Information Leaflet text

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxycodone Hydrochloride 10mg/ml Solution for Injection or Infusion
(referred to as Oxycodone Injection in this leaflet)

Read all of this leaflet carefully before you start to use this medicine.
- Keep this leaflet. You may need to read it again while you are receiving your treatment.
- If you have any further questions, please 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 get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Oxycodone Injection is and what it is used for
2. Before you use Oxycodone Injection
3. How to use Oxycodone Injection
4. Possible side effects
5. How to store Oxycodone Injection
6. Further Information

1. What Oxycodone Injection is and what it is used for

The name of your medicine is Oxycodone Injection.
Oxycodone belongs to a group of medicines known as opioid analgesics. These are strong painkillers (analgesics).

Oxycodone Injection is used in the treatment of pain requiring the use of a strong painkiller:
- moderate to severe pain in patients with cancer
- pain following an operation.

2. Before you use Oxycodone Injection

You should not use Oxycodone Injection if you:
- are allergic (hypersensitive) to oxycodone or to any of the other ingredients in Oxycodone Injection (see section 6, Further Information).
- are having difficulty breathing
- are taking drugs called monoamine oxidase inhibitors (MAOIs) for depression or have taken them in the last 2 weeks
- are pregnant
- have a head injury
- have a condition where your small bowel ceases to function (paralytic ileus)
- have moderate to severe liver or kidney disease
- suffer from a disease of the lung known as chronic obstructive pulmonary disease
- suffer from heart failure resulting from lung disease (cor pulmonale)
- suffer from chronic constipation
- suffer from asthma.

Talk to your doctor before using Oxycodone Injection if you:
- suffer from any problems with your breathing
- suffer from an underactive thyroid gland
- suffer from disease of the gall bladder and bile ducts
- suffer from inflammation of the bowel
- suffer from diseases of the adrenal glands
- suffer from pancreatitis
- have low blood pressure or low blood volume
- have toxic psychoses (mental illness as a reaction to drugs, toxins or severe illness)
- have an enlarged prostate gland
- have raised intracranial pressure
- have kidney or liver disease
- are intoxicated with alcohol
- are suffering from withdrawal symptoms of alcohol.

Special care should be taken with elderly, debilitated and infirm patients as well as patients with a history of drug or alcohol abuse. This medicine can cause dependence. If you have any concerns about whether this medicine is suitable for you speak to your doctor or nurse.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The following medicines can affect or be affected by treatment with Oxycodone Injection:
- tranquillizers and sleeping tablets
- anesthetics
- anti-depressants
- phenothiazines (often used to treat severe mental illness)
- neuroleptic drugs (often used to treat severe mental illnesses such as psychosis and schizophrenia)
- alcohol
- other opioid painkillers
- muscle relaxants
- monoamine oxidase inhibitors (MAOIs) (used in depression) – wait at least 2 weeks after stopping MAOIs before using this medicine.

Taking Oxycodone Injection with food and drink

As with all medicines that act on the central nervous system, it is advised that you do not drink alcohol while using this medicine.

Pregnancy and breast-feeding

You should not take this medicine if you are pregnant or breast-feeding. Babies born to women dependent on this medicine may experience withdrawal symptoms as well as breathing difficulties.

Driving and using machinery

Oxycodone Injection may cause drowsiness and reduced alertness, do not drive or operate machinery while using this medicine.

Important information about some of the ingredients in Oxycodone Injection

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

3. How to use Oxycodone Injection

Your doctor will determine the dose you require.
The usual doses in adults are:

- Injected into a vein as a single dose:
  - 10mg given slowly over 1 to 2 minutes
  - this dose may be repeated after 4 hours if required.
- Infusion through a drip in a vein:
  - starting dose 2mg/hour recommended.

Patient Controlled Analgesia (PCA) which allows the patient to top up the medicine when required
- single doses of 0.03mg per kg body weight should be used with a minimum lock-out time of five minutes.

- Injected under the skin as a single dose:
  - a starting dose of 1mg is recommended
  - repeat every 4 hours as required
  - Infusion through a drip under the skin:
  - in patients new to these painkillers a starting dose of 1mg/day is recommended, gradually increasing to control symptoms

- Cancer patients transferring to an infusion from oral oxycodone may require much higher doses.

Transferring patients from oral Oxycodone to Oxycodone Injection

The dose should be based on the following ratio (please note this is only a guide, the dose should be altered depending on patients response to treatment):

- 1mg of oral Oxycodone is equivalent to 1mg of Oxycodone Injection.

Elderly and patients with kidney and liver disease

The lowest dose needed for symptom control should be used.

Not to be used in patients under 18 years of age.
PAR Oxycodeone Hydrochloride 10 mg/ml Solution for Injection or Infusion PL 29831/0359; UK/H/2915/001/DC

If you take more Oxycodeone Injection than you should
This medicine will be given to you by your doctor so it is unlikely you will receive too much. Your doctor has information on how to recognise and treat an overdose.

If you stop using Oxycodeone Injection
Patients can become tolerant to the effects of oxycodone if used over a long time or if they are already using Oxycodeone and may require progressively higher doses in order to maintain pain control.

Prolonged use of this medicine may also lead to dependence and treatment is stopped abruptly patients may experience withdrawal symptoms. These symptoms include restlessness, runny nose and eyes, sweating, muscle pain, abdominal pain and diarrhoea.

When a patient no longer requires this medicine it is advised to stop treatment gradually over some time in order to prevent withdrawal symptoms.

4. Possible side effects
Like all medicines, Oxycodeone injection can cause side effects, although not everybody gets them. As can happen with any medicine, a few people may develop an allergic reaction. If you experience any of the following, seek medical help immediately:

- rash, itching, difficulty breathing.

Side effects that have been reported with Oxycodeone Injection are:

Very Common (more than 1 in 10 patients)
- sleepiness
- constipation
- vomiting

Common (occurs in more than 1 in 100 patients)
- abnormal thinking
- abnormal decrease in visual acuity
- headache
- abdominal pain
- diarrhoea
- dryness of mouth
- rash
- thirst
- problems passing water
- chills
- anxiety
- problems sleeping
- extreme fatigue
- nervousness
- anxiety

Uncommon (occurs in fewer than 1 in 100 patients)
- tremor
- fear
- constipation
- swelling of the lips
- depression
- problems walking
- mood changes
- vertigo
- depression
- involuntary movements
- increased muscle tone
- drug dependence
- unresponsiveness
- withdrawal
- running eyes
- abnormal vision
- abnormal heart rhythm
- blackouts
- nosebleeds
- voice alteration
- problems swallowing
- inflammation of stomach
- breathing
- gait bladder problems
- dry skin
- incontinence
- stops menstrual period
- allergy
- skin rash
- allergic reactions (severe allergy)

Some patients may develop a withdrawal symptom when treatment is stopped. Symptoms can include restlessness, secretion of tears, runny nose, yawning, perspiration, chills, muscle pain and prolonged dilation of the pupils.

If you experience any side effects or feel that the medicine is affecting you badly tell your doctor or nurse immediately.

5. How to store Oxycodeone Injection
Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.
- Do not use after the expiry date (shown on the packaging). The expiry date refers to the last day of the month, your doctor or nurse will check this.
- This medicine should be used immediately after opening.

Medicines should not be disposed of via wastewater or household waste. These measures will help protect the environment.

6. Further information
What Oxycodeone Injection contains
The active ingredient is oxycodone hydrochloride. Each ml contains oxycodone hydrochloride 10mg (equivalent to 8mg oxycodone base).

Each 1 ml ampoule contains oxycodone hydrochloride 10 mg (equivalent to 8 mg oxycodone base).
Each 2 ml contains oxycodone hydrochloride 20 mg (equivalent to 16 mg oxycodone base).

The other ingredients are: citric acid monohydrate, sodium citrate, sodium chloride, hydroxocitric acid, sodium hydroxide and water for injections.

What Oxycodeone Injection looks like and the contents of the pack
Oxycodeone Injection is a clear colourless solution and is supplied in packs of 6 containing either 1ml or 2ml clear glass ampoules.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Oxycodeone Hydrochloride 10mg/ml Solution for Injection or Infusion
Ireland: Oxycodeone Hydrochloride 10mg/ml Solution for Injection or Infusion
Cyprus: Oxycodeone Hydrochloride 10mg/ml Solution for Injection or Infusion
Malta: Oxycodeone Hydrochloride 10mg/ml Solution for Injection or Infusion
Poland: Oxycodeone Hydrochloride Wz-101

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 106 5000 (UK Only). Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product name</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone 10mg/ml Solution for Injection</td>
<td>PL 29831/0359</td>
</tr>
</tbody>
</table>

This is a service provided by the Royal National Institute of Blind People.

For the Republic of Ireland please call 3453 52 36253.

Leaflet Prepared: March 2010
1. NAME OF THE MEDICINAL PRODUCT
Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains oxycodone hydrochloride 10 mg (equivalent to 8 mg of oxycodone base).
Each 1 ml ampoule contains oxycodone hydrochloride 10 mg (equivalent to 6 mg of oxycodone base).
Each 2 ml ampoule contains oxycodone hydrochloride 20 mg (equivalent to 16 mg of oxycodone base).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose.
For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection or infusion (injection or infusion).

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.

4.2 Pharmacology and method of administration
Route of administration:
Subcutaneous injection or infusion.

Intravenous injection or infusion.

Pharmacology:
The dose should be adjusted according to the severity of pain, the total condition of the patient and previous or concurrent medication.

Adults over 18 years:
The following starting doses are recommended. A gradual increase in dose may be required in analgesia that is inadequate or if pain severity increases.

i.v. (Bolus): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Administer a bolus dose of 1 to 10 mg slowly over one to two minutes minutes.

Doses should not be administered more frequently than every four hours.

i.v. (Infusion): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. A starting dose of 2 mg/hour is recommended.

i.v. (PCA): Dilute to 1 mg/ml in 0.9% saline, 5% dextrose or water for injections. Bolus doses of 0.35 mg/kg should be administered with a minimum lock-out time of five minutes.

s.c. (Bolus): Use as 10 mg/ml concentration. A starting dose of 5 mg is recommended, repeated at four-hourly intervals as required.

s.c. (Infusion): Dilute in 0.9% saline, 5% dextrose or water for injections if required. A starting dose of 7.5 mg/day is recommended in opioid-naive patients, titrating gradually according to symptom control. Cancer patients transferring from oral oxycodone may require much higher doses (see below).

Transferring patients between oral and parenteral oxycodone:
The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly:
Elderly patients should be treated with caution. The lowest dose should be administered with careful titration to pain control.

Patients with renal and hepatic impairment:
Patients with mild to moderate renal impairment and/or mild hepatic impairment should be treated with caution. The lowest dose should be given with careful titration to pain control.

Children under 18 years:
There are no data on the use of Oxycodone injection in patients under 15 years of age.

Use in non-malignant pain:
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and interventional disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

Contraindications:
Oxycodone injection is contraindicated in patients with known hypersensitivity to oxycodone or any of the other constituents, or in any situation where opioids are contraindicated, respiratory depression, head injury, paralytic ileus, acute abdomen, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypertension, moderate to severe hepatic impairment; severe renal impairment (creatinine clearance <10 ml/min), chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use; pregnancy, lactation.

4.4 Special warnings and precautions for use
The major risk of opioid excess is respiratory depression. As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychoses, diseases of the biliary tract, inflammatory bowel disorders, pre-existing hypothyroidism, addisonian insufficiency, acute alcoholism, delirium tremens, pancreatitis, chronic renal and hepatic disease or severe pulmonary disease and debilitated, elderly and infants patients. Oxycodone injection should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxycodone injection should be discontinued immediately.

The patient may develop tolerance to oxycodone with chronic use and require progressively higher doses to maintain pain control. The patient may develop physical dependence, in which case an alcoholism syndrome may be seen following abrupt cessation.

For appropriate patients who suffer from chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history. Oxycodone injection should be used with particular care in patients with a history of alcohol and drug abuse.

If opioid treatment is considered appropriate for the patient, then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate
pain relief with a minimum of side effects. There must be frequent contact between physician and patient so that dosage adjustments can be made. It is strongly recommended that the physician defines treatment outcomes in accordance with pain management guidelines. The physician and patient can then agree to discontinue treatment if these objectives are not met.

Oxycodone has an abuse liability similar to other strong opioids and should be used with caution in opioid-dependent patients. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

Oxycodone injection contains approximately 5mg sodium per ml i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There is an enhanced CNS depressant effect with drugs such as tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis.

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. While these pathways may be blocked by a variety of drugs, such blockade has not yet been shown to be of clinical significance with this agent.

4.6 Pregnancy and lactation

Pregnancy

The effect of oxycodone in human reproduction has not been adequately studied. No studies on fertility or the post-natal effects of intrauterine exposure have been carried out. However, studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult dose of 160 mg/day, respectively, did not reveal evidence of harm to the foetus due to oxycodone. Oxycodone injection is not recommended for use in pregnancy nor during labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Lactation

Oxycodone is secreted in breast milk and may cause harmful effects in the newborn (respiratory depression, somnolence, lethargy). Oxycodone is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. Therefore patients should not drive or operate machinery, if affected.

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Tolerance and Dependence, below). Constipation may be prevented with an appropriate laxative. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic.
Oxycodeone Hydrochloride 10 mg/ml Solution for Injection or Infusion

The adverse drug reactions seen whilst being treated with oxycodone were:

**Endocrine disorders:**
Uncommon >1/1,000, <1/100): syndrome of inappropriate antidiuretic hormone secretion.

**Metabolism and nutrition disorders:**
Common >1/100, <1/10): anorexia.

**Uncommon >1/1,000, <1/100): dehydration, weight change, peripheral oedema, oedema, thirst.**

**Psychiatric disorders (see Tolerance and dependence below):**
Common >1/100, <1/10): abnormal dreams, anxiety, confusion, insomnia, nervousness, abnormal thinking.

**Nervous system disorders:**
Very common >1/10: somnolence, dizziness.

**Common >1/100, <1/10): dizziness, headache.**

**Uncommon >1/1,000, <1/100): abnormal gait, anorexia, hyperkinesia, hypertonia, hypoaesthesia, hypotonia, speech disorder, stupor, tremor, twitching, vertigo, epileptic seizures, parasthesia, withdrawal syndrome, malaise, muscle contractions involuntary.**

**Eye disorders:**
Uncommon >1/1,000, <1/100): lacrimation disorder, miosis, abnormal vision.

**Uncommon >1/1,000, <1/100): tinnitus.**

**Cardiovascular disorders:**
Common >1/100, <1/10): orthostatic hypotension.

**Vascular disorders:**
Uncommon >1/1,000, <1/100): palpitations (in the context of withdrawal syndrome), hypotension, syncope.

**Respiratory, thoracic and mediastinal disorders:**
Uncommon >1/1,000, <1/100): vasodilatation.

**Common >1/100, <1/10): dyspnoea, brachyphalaxia.**

**Uncommon >1/1,000, <1/100): rhinitis, epistaxis, hiccup, voice alteration, respiratory depression.**

**Gastrointestinal disorders:**
Very common >1/10): constipation, nausea, vomiting.

**Common >1/100, <1/10): abdominal pain, anorexia, diarrhoea, dry mouth, dyspepsia.**

**Uncommon >1/1,000, <1/100): dyspnoea, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis, bilateral spasm, gastrointestinal disorders, taste perversion.**

**Skin and subcutaneous tissue disorders:**
Very common >1/10): pruritus.

**Common >1/100, <1/10): rash, sweating.**

**Uncommon >1/1,000, <1/100): dry skin, urticaria.**

**Renal and urinary disorders:**
Common >1/100, <1/10): urinary disorders.

Uncommon >1/1,000, <1/100): urinary retention, ureteral spasm.

**Reproductive and breast disorders:**
Uncommon >1/1,000, <1/100): impotence, amenorrhea.

**General disorders and administration site conditions:**
Common >1/100, <1/10): fever, chills.

**Uncommon >1/1,000, <1/100): chest pain, allergic reaction, anaphylactic reaction, anaphylactoid reaction, drug dependence.**

**Tolerance and Dependence:**

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of oxycodone injection may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, miosis, yawning, perspiration, chills, myalgia and rhinorrhea. Other symptoms may also develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

The development of psychological dependence (addiction) to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of psychological dependence (addiction) in chronic pain patients.

Oxycodone injection should be used with particular care in patients with a history of alcohol and drug abuse.

4.9 Overdose

**Symptoms of overdosage**

Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression, hypotension and hallucinations. Nausea and vomiting are common in less severe cases. Non-cardio pulmonary oedema and rhabdomyolysis are particularly common after intravenous injection of opioid analgesics. Circulatory failure and somnolence progressing to stupor or coma, skeletal muscle fasciculation, bradycardia and death may occur in more severe cases.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic drugs.

**Treatment of overdosage**

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2mg for an adult and 0.01mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If naloxone is required than an infusion of 80% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml of saline will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient’s clinical state.

Intravenous naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respirations are reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.
For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

The patient should be observed for at least 6 hours after the last dose of naloxone.

Naloxone should not be administered in the absence of clinically significant respiratory or cardiovascular depression secondary to oxycodone overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological group: Natural eugam alkaloids

ATC code: N02A A06

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opioid receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic, antitusive and sedative.

Opioids may influence the hypothalamic-pituitary-gonadal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifested from these hormonal changes.

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from oxycodone injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 6 hours.

Following absorption, oxycodone is distributed throughout the entire body. Approximately 40% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphine and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant.

The active drug and its metabolites are excreted in both urine and faeces.

The plasma concentrations of oxycodone are only minimally affected by age, being 10% greater in elderly as compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis.

The drug penetrates the placenta and can be found in breast milk.

When compared to normal subjects, patients with mild to severe hepatic dysfunction may have higher plasma concentrations of oxycodone and noroxycodone, and lower plasma concentrations of oxymorphine. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

When compared to normal subjects, patients with mild to severe renal dysfunction may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone and this may be accompanied by an increase in drug effects.

5.3 Preclinical safety data

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation) and with activation after 48 hours of exposure) at doses of up to 1000 μg/ml, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 46 μg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosome aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/ml or greater with metabolic activation and at 400 μg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glicolic acid monohydrate
Sodium chloride
Sodium oleate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.3.

Cyclazoline at concentrations of 3 mg/ml or less, when mixed with oxycodone injection, either undiluted or diluted with water for injection, shows no sign of precipitation over a period of 24 hours storage at room temperature. The solution has been shown to occur in mixtures with oxycodone injection at cyclazoline concentrations greater than 3 mg/ml or when diluted with 0.9% saline. It is recommended that water for injection be used as a diluent when cyclazoline and oxycodone hydrochloride are co-administered either intravenously or subcutaneously as an infusion.

Preparations made with oxycodone injection should be administered either intravenously or subcutaneously as an infusion.

6.3 Shelf life

Unopened, 2 years.

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded. Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and will normally not be longer than 24 hours at 2 to 8°C, unless reconstitution, dilution, etc. is taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Type 1 clear glass ampoules: 1 ml and 2 ml.
Pack size: 5 ampoules.

6.6 Special precautions for disposal

Oxycodone injection has been shown to be compatible with the following drugs:

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride

Oxycodone injection, undiluted or diluted to 1 mg/ml with 0.9% w/v saline, 5% w/v dextrose or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags, over a 24 hour period at room temperature.

The injection, whether undiluted or diluted to 1 mg/ml in the infusion fluids used in these studies and contained in the various assemblies, does not need to be protected from light.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0359
PA 1339/25/1
MA 154/05/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
Module 4

Labelling text

10mg/1ml and 20mg/2ml presentations - carton and immediate label

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

Oxycodone Hydrochloride 10mg/ml Solution for Injection or Infusion

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

10mg in 1ml

or

20mg in 2ml

Each ampoule contains 10mg or 20mg of oxycodone hydrochloride in 1ml or 2ml of solution.

3. **LIST OF EXCIPIENTS**

Other ingredients: sodium citrate, citric acid monohydrate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

Contains sodium. Read the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Solution for injection or infusion

5 ampoules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For subcutaneous or intravenous use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

(overprinted)
9. SPECIAL STORAGE CONDITIONS

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0359
PA 1339/25/1
MA 154/05101

13. BATCH NUMBER

(overprinted)

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

CD

15. INSTRUCTIONS ON USE

Dose: As directed by the doctor.
Read the package leaflet before use.

16. INFORMATION IN BRAILLE

(n/a)

Other:

Affix dispensing label here
Manufacturing date (overprinted if applicable)
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT

Oxycodone Hydrochloride 10mg/ml Injection or Infusion

| 10mg in 1ml |

or

| 20mg in 2ml |

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

(overprinted)

4. BATCH NUMBER

(overprinted)

5. OTHER

For sc or iv use
PL 29831/0359
PA 1339/25/1

Manufacturing date (overprinted if applicable)
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Wockhardt UK Limited a Marketing Authorisation for the medicinal product Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion (PL 29831/0359, UK/H/2915/001/DC) on 7th May 2010. The product is a prescription-only medicine.

This is an abridged application for Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, submitted under Article 10.1 of 2001/83 EC, as amended. The application refers to OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128), authorised to Napp Pharmaceuticals Limited in the UK on 14th April 2003. Napp Pharmaceuticals Limited holds a licence for Oxycontin® 10mg prolonged-release tablets, for the same active substance, granted in Ireland on 28th May 1998. The EU originator product, Oxycontin® 10mg prolonged-release tablets, has been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired. With the UK as the Reference Member State in this Decentralised Procedure, Wockhardt UK Limited applied for a Marketing Authorisation for Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion in Cyprus, Ireland, Malta and Poland.

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain; and for the treatment of severe pain requiring the use of a strong opioid.

Oxycodone belongs to the pharmacotherapeutic group, natural opium alkaloids (ATC code - N02A A05). Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opioid receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from oxycodone injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours. Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphone and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant. The active drug and its metabolites are excreted in both urine and faeces.

The medicinal product is presented as a clear, colourless solution for injection or infusion. It must not be mixed with other medicinal products except those mentioned in section 6.6 of the SmPC. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.
No new pre-clinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.
II. **ABOUT THE PRODUCT**

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion</th>
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<td>Oxycodone hydrochloride</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Natural opium alkaloids (N02A A05)</td>
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<td>Solution for injection or infusion (10 mg/ml)</td>
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</tr>
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<td>Member States concerned</td>
<td>CY, IE, MT, PL</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0359</td>
</tr>
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| Name and address of the authorisation holder    | Wockhardt UK Ltd  
Ash Road North  
Wrexham  
LL13 9UF  
UK                                                                                       |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Oxycodone hydrochloride

Nomenclature:
INN: Oxycodone hydrochloride
Chemical names: 4,5a-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Structure:

Molecular formula: \( \text{C}_{18}\text{H}_{22}\text{ClNO}_4 \cdot \text{HCl} \)
Molecular weight: 351.9 g/mol
CAS No: 124-90-3
Physical form: White or almost white powder, hygroscopic
Solubility: Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene

The active substance, oxycodone hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of oxycodone hydrochloride are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of oxycodone hydrochloride for inclusion in this medicinal product.

The current CEP states a re-test period of 5 years for the active substance.
MEDICINAL PRODUCT

Other ingredients

The finished product is presented as a clear, colourless, sterile solution of oxycodone hydrochloride in water for injections. Each 1ml dose contains 10mg oxycodone hydrochloride, equivalent to 9mg/ml oxycodone base.

Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of sodium hydroxide and hydrochloric acid, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory. The objective was to develop a stable formulation for oxycodone hydrochloride 10mg/ml solution for injection or infusion, in 1ml and 2ml glass ampoules, with similar physical and chemical characteristics to the comparator product Oxynorm® 10mg/ml solution for injection or infusion supplied by Napp Pharmaceuticals Ltd.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data were provided and all data were within specification.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for two batches of the finished product, presented in both 1ml and 2ml ampoules. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in clear, colourless Type I glass ampoules of volume 1ml or 2ml. The ampoules contain 1ml or 2ml of sterile solution of oxycodone hydrochloride (concentration 10 mg/ml).
The ampoules are packaged with the Product Information Leaflet (PIL) into cardboard outer cartons, in pack sizes of 5. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the unopened ampoule, which is satisfactory. The injection should be given immediately after opening the ampoule. This medicinal product does not require any special storage conditions. For further advice for use of the opened ampoule, refer to section 6.3 of the SmPC. Please also refer to the SmPC for information on compatible or incompatible products, and handling of this product.

**Bioequivalence Study**

Bioequivalence studies are not necessary to support this application for a parenteral product.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved SmPC, and labelling and leaflet texts are satisfactory. The MAH has committed to submitting mock-ups for the packaging and PIL for assessment before packs are commercially marketed.

**Conclusion**

The proposed product, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, has been shown to be a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, and the originator product, Oxycontin® 10mg prolonged-release tablets, has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

**III.2 NON-CLINICAL ASPECTS**

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of oxycodone hydrochloride, which is a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, OxyNorm® 10mg/ml solution for injection or infusion (Napp Pharmaceuticals Limited).
III.3 CLINICAL ASPECTS

INDICATIONS
Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain; and for the treatment of severe pain requiring the use of a strong opioid.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of oxycodone hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of oxycodone hydrochloride is well-established from its extensive use in clinical practice.

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited). Thus, in accordance with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Clinical safety
No novel safety data have been submitted and none are required for applications of this type. The safety profile of oxycodone hydrochloride is well-known. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product, and is acceptable.

Product Information Leaflet (PIL)
The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling
The labelling text is satisfactory.
Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Post marketing experience
No post-marketing data are available. The medicinal product has not been marketed in any country. Oxycodone has a well-recognised efficacy and an acceptable level of safety in the approved indications.

CONCLUSIONS & DISCUSSION
The grounds for establishing the proposed product, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, as a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the applicant. When used as indicated, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was therefore recommended on clinical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-ClinICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
The applicant’s Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion has been demonstrated to be a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling texts are satisfactory and consistent with those for the reference product.

The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for the packaging and PIL for assessment before packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion and the reference product, OxyNorm® 10mg/ml solution for injection or infusion (Napp Pharmaceuticals Limited), are interchangeable. Extensive clinical experience with oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

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<th>Scope</th>
<th>Outcome</th>
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