Public Assessment Report

Decentralised Procedure

Oxycodone Hydrochloride 5 mg/5 ml Oral Solution
Oxycodone Hydrochloride 10 mg/ml Oral Solution

UK/H/2780/001-2/DC

UK licence no: PL 29831/0458-9

Wockhardt UK Ltd
LAY SUMMARY

On 25 May 2011, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Oxycodone Hydrochloride 5mg/5ml Oral Solution (PL 29831/0458) and Oxycodone Hydrochloride 10mg/ml Oral Solution (PL 29831/0459). These licences were granted via the decentralised procedure (UK/H/2780/001-002/DC), with the UK as the Reference Member State (RMS) and Malta as the Concerned Member State (CMS).

Oxycodone Hydrochloride belongs to a group of medicines known as opioid analgesics. These are strong painkillers (analgesics). Oxycodone Hydrochloride is used in the treatment of moderate to severe pain in patients with cancer as well as treating post-operative pain.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

| **Product Name** | Oxycodone Hydrochloride 5 mg/5 ml Oral Solution  
|                 | Oxycodone Hydrochloride 10 mg/ml Oral Solution |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | Oxycodone Hydrochloride |
| **Form** | Oral Solution |
| **Strength** | 1 mg/ml (5 mg/5 ml)  
| | 10 mg/ml |
| **Marketing Authorisation Holder** | Wockhardt UK Ltd  
| | Ash Road North, Wrexham, LL13 9UF  
| | United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Malta |
| **Procedure Number** | UK/H/2780/01-02/DC |
| **End of Procedure** | 17th April 2011 |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Oxycodone Hydrochloride 5mg/5ml Oral Solution (PL 29831/0458) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Oxycodone Hydrochloride 5mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml contains oxycodone hydrochloride 5 mg (equivalent to 4.5 mg of oxycodone base).

This medicinal product contains approximately 3.5mg sodium per 5ml.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
A clear, colourless oral solution.

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:
Oral use.

Post-operative pain:
In common with other strong opioids, the need for continued treatment should be assessed at regular intervals.

Elderly and adults over 18 years:
Oxycodone solution should be taken at 4-6 hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Increasing severity of pain will require an increased dosage of Oxycodone solution. The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosing period. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 5 mg, 4-6 hourly. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of Oxycodone solution required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Adults with mild to moderate renal impairment and mild hepatic impairment:
The plasma concentration in this patient population may be increased. Therefore, dose initiation should follow a conservative approach. The starting dose for opioid naïve patients is 2.5 mg, 6-hourly.

Children under 18 years:
Oxycodone solution should not be used in patients under 18 years.
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
Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity or in any situation where opioids are contra-indicated, 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 and lactation, hypersensitivity to any of the constituents of the product.

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

As with all opioid preparations, patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxycodone solution for 6 hours prior to the intervention. If further treatment with oxycodone is indicated then the dosage should be adjusted to the new post-operative requirement.
Oxycodone should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

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 solution 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 profile similar to other strong opioids. 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.

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

Oxycodone 5mg/5ml solution contains approximately 3.5mg sodium per 5ml. A total daily dose of 400mg of this product contains approximately 277mg sodium. To be taken into consideration in patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Oxycodone, like other opioids, potentiates the effects of 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.

Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6 with a modified release oxycodone tablet, resulted in an increase in oxycodone $C_{\text{max}}$ by 11%, AUC by 13%, and $t_{1/2}$ elim. by 14%. Also an increase in noroxycodone level was observed, ($C_{\text{max}}$ by 50%, AUC by 85%, and $t_{1/2}$ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme. Cimetidine and inhibitors of cytochrome P450-3A4 such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone.

4.6 Pregnancy and lactation

Pregnancy
Oxycodone solution is not recommended for use during pregnancy nor during labour (see section 4.3). There are no adequate data from the use of oxycodone in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Oxycodone crosses the placenta. Prolonged use of oxycodone during pregnancy can cause withdrawal symptoms in newborns. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Lactation
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone solution is contraindicated during breast-feeding (see section 4.3).

Fertility
There are no data on the effects of oxycodone on fertility (see section 5.3).

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 anti-emetic. Common (incidence of $\geq 1\%$) and uncommon (incidence of $\leq 1\%$) adverse drug reactions are listed in the table below.

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Renal and urinary disorders | Urinary disorders | Urinary retention
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| | | Ureteral spasm
| Reproductive system and breast disorders | Amenorrhoea | Libert decreased
| | | Erectile dysfunction
| General disorders and administration site conditions | Asthenia | Drug tolerance
| | | Chills
| | | Oedema
| | | Oedema peripheral
| | Malaise
| | Thirst
| | Pyrexia
| | Drug withdrawal syndrome

**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 solution 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, rhinorhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

**4.9 Overdose**
Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases. **Treatment of oxycodone 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 2 mg for an adult and 0.01 mg/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 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 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.
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. **Additional/other considerations:**
• Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.
• Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.

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
Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration. Oxycodone has an elimination half-life of approximately 3-4 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma at low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

A pharmacokinetic study in healthy volunteers has demonstrated that, following administration of a single 10 mg dose, oxycodone solution provided an equivalent rate and extent of absorption of oxycodone. Mean peak plasma concentrations of approximately 20 ng/ml were achieved within 1.5 hours of administration, median $t_{max}$ values from both strengths of liquid being less than one hour.

Studies involving controlled release oxycodone have demonstrated that the oral bioavailability of oxycodone is only slightly increased (16%) in the elderly. In patients with renal and hepatic impairment, the bioavailability of oxycodone was increased by 60% and 90% respectively, and a reduced initial dose is recommended in these groups.

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.

There is insufficient data on the reproduction toxicity properties of oxycodone and there are no studies on fertility or the post-natal effects following intrauterine exposure. 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 fetus due to oxycodone.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Citric acid monohydrate
Sodium citrate
Sodium benzoate
Sodium saccharin
Hypromellose (methocel-E15 premium LV)
Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Unopened: 18 months.
After first opening: 1 month

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package in order to protect from light

6.5 Nature and contents of container
Oxycodone solution is supplied in 250 ml amber soda glass (type III) bottles, fitted with 28 mm white child resistant tamper evident caps with expanded polyethylene (EPE) liners, contained in outer cardboard cartons.

6.6 Special precautions for disposal
No special requirements

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0458

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2011

10 DATE OF REVISION OF THE TEXT
25/05/2011
The UK Summary of Product Characteristics (SmPC) for Oxycodone Hydrochloride 10mg/ml Oral Solution (PL 29831/0459) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Oxycodone Hydrochloride 10mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1ml contains oxycodone hydrochloride 10 mg (equivalent to 9 mg of oxycodone base).

This medicinal product contains approximately 0.85mg sodium per ml.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
A clear, orange oral solution.

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:
Oral use.

Post-operative pain:
In common with other strong opioids, the need for continued treatment should be assessed at regular intervals.

Elderly and adults over 18 years:
Oxycodone solution should be taken at 4-6 hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Increasing severity of pain will require an increased dosage of Oxycodone solution. The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosing period. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 5 mg, 4-6 hourly. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of Oxycodone solution required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Adults with mild to moderate renal impairment and mild hepatic impairment:
The plasma concentration in this patient population may be increased. Therefore, dose initiation should follow a conservative approach. The starting dose for opioid naïve patients is 2.5 mg, 6-hourly.

Children under 18 years:
Oxycodone solution should not be used in patients under 18 years.

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
Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity or in any situation where opioids are contra-indicated, 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 and lactation, hypersensitivity to any of the constituents of the product.

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

As with all opioid preparations, patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxycodone solution for 6 hours prior to the intervention. If further treatment with oxycodone is indicated then the dosage should be adjusted to the new post-operative requirement.

Oxycodone should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

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 solution 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 profile similar to other strong opioids. 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.

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

Oxycodone 10mg/ml solution contains approximately 0.85mg sodium per ml. A total daily dose of 400mg of this product contains approximately 34mg sodium. To be taken into consideration in patients on a controlled sodium diet.

Oxycodone 10mg/ml solution contains sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
Oxycodone, like other opioids, potentiates the effects of 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.
Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6 with a modified release oxycodone tablet, resulted in an increase in oxycodone $C_{\text{max}}$ by 11%, AUC by 13%, and $t_{\text{1/2}}$ elim. by 14%. Also an increase in noroxycodone level was observed, ($C_{\text{max}}$ by 50%, AUC by 85%, and $t_{\text{1/2}}$ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme. Cimetidine and inhibitors of cytochrome P450-3A4 such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone.

4.6 Pregnancy and lactation

Pregnancy

Oxycodone solution is not recommended for use during pregnancy nor during labour (see section 4.3). There are no adequate data from the use of oxycodone in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Oxycodone crosses the placenta. Prolonged use of oxycodone during pregnancy can cause withdrawal symptoms in newborns. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Lactation

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone solution is contraindicated during breast-feeding (see section 4.3).

Fertility

There are no data on the effects of oxycodone on fertility (see section 5.3).

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 anti-emetic. Common (incidence of ≥1%) and uncommon (incidence of ≤1%) adverse drug reactions are listed in the table below.

<table>
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<tr>
<th>Body System</th>
<th>Common</th>
<th>Uncommon</th>
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<td>Lacrimation disorder</td>
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<td>Vascular disorders</td>
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<td>Renal and urinary disorders</td>
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<td>General disorders and administration site</td>
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### Conditions

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<td>Pyrexia</td>
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<td>Drug withdrawal syndrome</td>
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</table>

**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 solution 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, mydriasis and palpitations. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

### 4.9 Overdose

Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases.

*Treatment of oxycodone 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 2 mg for an adult and 0.01 mg/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 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 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.

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.

**Additional/other considerations:**

- Consider activated charcoal (50 g for adults, 10 -15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.
- Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.
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

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration. Oxycodone has an elimination half life of approximately 3-4 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma at low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

A pharmacokinetic study in healthy volunteers has demonstrated that, following administration of a single 10 mg dose, oxycodone solution provided an equivalent rate and extent of absorption of oxycodone. Mean peak plasma concentrations of approximately 20 ng/ml were achieved within 1.5 hours of administration, median $t_{\text{max}}$ values from both strengths of liquid being less than one hour.

Studies involving controlled release oxycodone have demonstrated that the oral bioavailability of oxycodone is only slightly increased (16%) in the elderly. In patients with renal and hepatic impairment, the bioavailability of oxycodone was increased by 60% and 90% respectively, and a reduced initial dose is recommended in these groups.

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.

There is insufficient data on the reproduction toxicity properties of oxycodone and there are no studies on fertility or the post-natal effects following intrauterine exposure. 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 fetus due to oxycodone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium benzoate
Sodium saccharin
Sunset yellow (E110)
Purified water
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
Unopened: 18 months.
After first opening: 1 month.

6.4 **Special precautions for storage**
Do not store above 25°C.
Store in the original package in order to protect from light.

6.5 **Nature and contents of container**
Oxycodone solution is supplied in 125 ml amber soda glass (type III) bottles, fitted with 28 mm white child resistant tamper evident caps with expanded polyethylene (EPE) liners, contained in outer cardboard cartons. In addition a 3ml dosing dispenser and a bottle adapter will be supplied with each pack.

6.6 **Special precautions for disposal**
No special requirements.

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

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 29831/0459

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
25/05/2011

10 **DATE OF REVISION OF THE TEXT**
25/05/2011
Module 3
Product Information Leaflet

1. What Oxycodeone 5mg/5ml Solution is and what it is used for

The name of your medicine is Oxycodeone 5mg/5ml Solution. Oxycodeone belongs to a group of medicines known as opioid analgesics. These are strong painkillers (analgesics).

Oxycodeone 5mg/5ml Solution 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.

You should not take Oxycodeone 5mg/5ml Solution if you:
- are allergic (hypersensitive) to oxycodeone or to any of the other ingredients in Oxycodeone 5mg/5ml Solution (see section 6, Further Information).
- are having difficulty breathing
- are taking drugs called monoamine oxidase inhibitors (MAOIs) for depression (examples include tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid) or have taken them in the last 6 weeks
- are pregnant or breastfeeding
- have had an injury that causes a severe headache or makes you feel sick. This is because this medicine may make these symptoms worse or hide the extent of the head injury
- have a condition where your small bowel ceases to function (paralytic ileus), your stomach empties more slowly than it should (delayed gastric emptying) or you have a severe pain in your abdomen
- have moderate to severe liver or kidney disease
- have an abnormally high level of carbon dioxide circulating in the blood (a condition known as hypercapnia)
- suffer from a disease of the lung known as chronic obstructive pulmonary disease
- suffer from heart failure resulting from lung disease (or pneumoconiosis)
- suffer from chronic constipation
- suffer from asthma.

Tell your doctor before using Oxycodeone 5mg/5ml Solution if you:
- suffer from any problems with your breathing
- suffer from an undervactive 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 (inflammation of the pancreas, which causes severe pain in the abdomen and back)
- have low blood pressure or low blood volume
- have had psychosis (mental illness as a reaction to drugs, toxins or severe illness)
- have an enlarged prostate gland
- have a severe headache or feel sick as this may indicate that the pressure in your skull is increased (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 weak 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.

If you are going to have an operation, please tell the doctor at the hospital that you are taking this medicine.

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 Oxycodeone 5mg/5ml Solution:
- tranquilizers and sleeping tablets
- anesthetics
- anti-depressants
- antidepressants
- phenothiazines (often used to treat severe mental illness)
- other anesthetic drugs (often used to treat severe mental illnesses such as psychosis and schizophrenia)
- alcohol
- other opioid painkillers
- muscle relaxants
- medicines to treat high blood pressure
- quinidine (a medicine to treat a fast heart beat)
- clindamycin (a medicine for stomach ulcers, indigestion or heartburn)
- antifungal medicines (such as ketoconazole)
- antibiotics (such as erythromycin)
- monoamine oxidase inhibitors (MAOIs) used in depression — wait at least 2 weeks after stopping MAOIs before using this medicine.

Taking Oxycodeone 5mg/5ml Solution 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 taking 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
Oxycodeone 5mg/5ml Solution may cause dizziness and reduced alertness, do not drive or operate machinery while taking this medicine.

Important information about some of the ingredients in Oxycodeone 5mg/5ml Solution
A total daily dose of 40gml of this medicine contains approximately 277mg sodium. To be taken into consideration in patients on a controlled sodium diet.

3. How to take Oxycodeone 5mg/5ml Solution

Your doctor will determine the dose you require.

A child (over 18 years of age)
The usual starting dose is 5mg every four to six hours. However, your doctor will prescribe the dose required to treat your pain. If you find that you are still in pain whilst taking this medicine discuss this with your doctor.

Patients with kidney and liver disease
The dosage should follow a conservative approach. The usual starting dose is 2.5mg every 6 hours. Do not exceed the dose recommended by your doctor.

You must only take this medicine by mouth. This medicine should never be injected as this may lead to serious side effects, which may be fatal.

19/02/201
PAR Oxycodeone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution

UK/H/2780/001-2/DC

Net to be used in patients under 18 years of age.

If you take more Oxycodeone 5mg/5ml Solution than you should
Call your doctor or hospital immediately. People who have taken an overdose may feel very sleepy, sick or dizzy. They may also have breathing difficulties leading to unconsciousness or even death and may need emergency treatment in hospital. Make sure you take this leaflet and any other remaining medicine with you to show the doctor.

If you forget to take Oxycodeone 5mg/5ml Solution
If you miss a dose you should take the next dose as soon as you remember it and carry on as before. Do not take two doses in four hours. Do not take a double dose to make up for a forgotten dose.

If you stop taking Oxycodeone 5mg/5ml Solution
Patients can become tolerant to the effects of oxycodeone if used over a long time or if they are already using oxycodeone and may require progressively higher doses in order to maintain a pain control.

Prolonged use of this medicine may lead to dependence and if treatment is stopped abruptly you may experience withdrawal symptoms. These symptoms include restlessness, running nose and eyes, yawning, sweating, chills, muscle pain, abdominal pain, diarrhoea and prolonged dilatation of the pupils.

You should not suddenly stop taking this medicine unless your doctor tells you to. If you want to stop taking this medicine, discuss this with your doctor first. They will tell you to stop treatment gradually over some time.

5. Possible side effects
Like all medicines, Oxycodeone 5mg/5ml Solution 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, problems swallowing, anaphylaxis (severe allergy).

Side effects that have been reported with Oxycodeone 5mg/5ml Solution are:

- Common (occurs in more than 1 in 100 patients)
  - tiredness
  - constipation
  - vomiting
  - abdominal pain
  - diarrhoea
  - loss of appetite
  - nausea
  - dry mouth
  - rash
  - fever
  - abnormal dreams
  - anorexia

- Uncommon (occurs in fewer than 1 in 100 patients)
  - weight change
  - decreased sex drive
  - hallucinations
  - memory loss
  - fits
  - euphoria
  - twitching
  - speech problems
  - decreased muscle tone
  - excitement
  - palpitations
  - general malaise

- Unknown
  - involuntary movements
  - increased muscle tone
  - drug dependence
  - unresponsiveness
  - withdrawal
  - running eyes
  - problems swallowing
  - inflammation of stomach
  - feeling
  - menstrual period
  - allergy
  - charged or reduced sensitivity
  - inability to pass water
  - increase in liver enzymes

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 5mg/ml Solution
Keep out of the reach of children.
• Do not store above 25°C.
• Store in the original package in order to protect from light. 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 for this.
• Once opened this medicine must be used within 1 month.
• Consult a pharmacist if signs of deterioration of the product are observed.

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

6. Further information
What Oxycodeone 5mg/5ml Solution contains
The active ingredient is oxycodone hydrochloride. Each 5ml contains oxycodone hydrochloride 5mg (equivalent to 4.5mg oxycodone base).

The other ingredients are: citric acid monohydrate, sodium citrate, sodium benzoate, sodium saccharide, hypromellose (methoacrylate 15 prem unmethoacrylate), purified water.

What Oxycodeone 5mg/5ml Solution looks like and the contents of the pack
This is a clear colourless solution. Each bottle contains 250ml of solution.

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 5mg/5ml Oral Solution
Malta: Oxycodeone Hydrochloride 5mg/5ml Oral Solution

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 195 5000 (UK Only). Please be ready to give the following information:

Product name Reference number
Oxycodeone Hydrochloride 5mg/5ml Oral Solution PL 23831/04/38

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

Leaflet Prepared: March 2011

WOCHARDT
Package Leaflet: Information for the User
Oxycodone Hydrochloride 10mg/ml Oral Solution

Refer to as Oxycodone 10mg/ml Solution 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 serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Oxycodone 10mg/ml Solution is and what it is used for
2. Before you take Oxycodone 10mg/ml Solution
3. How to take Oxycodone 10mg/ml Solution
4. Possible side effects
5. How to store Oxycodone 10mg/ml Solution
6. Further information

1. What Oxycodone 10mg/ml Solution is and what it is used for

The name of your medicine is Oxycodone 10mg/ml Solution. This medicine belongs to a group of medicines known as opioid analgesics. These are strong painkillers (analgesics). Oxycodone 10mg/ml Solution 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.

You should not take Oxycodone 10mg/ml Solution if you:
- are allergic (hypersensitive) to oxycodone or any of the other ingredients in Oxycodone 10mg/ml Solution (see Section 6, Further information)
- are having difficulty breathing
- are taking other drugs called monoamine oxidase inhibitors (MAOIs) for depression (examples include tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid) or have taken them in the last 2 weeks
- are pregnant or breastfeeding
- have a head injury that causes a severe headache or makes you feel sick. This is because this medicine may make these symptoms worse or hide the extent of the head injury
- have a condition where your small bowel causes to function (paralytic ileus), your stomach empties more slowly than it should (delayed gastric emptying) or you have a severe pain in your abdomen
- have severe unconsciousness, or you have a severe liver or kidney disease
- have an abnormal high level of carbon dioxide circulating in the blood (a condition known as hypercapnia)
- suffer from a disease of the lung known as chronic obstructive pulmonary disease
- suffer from heart failure resulting from lung disease (congestive heart failure)
- suffer from chronic constipation
- suffer from asthma.

Talk to your doctor before using Oxycodone 10mg/ml Solution if you:
- suffer from any problems with your breathing
- suffer from an underactive thyroid gland
- suffer from disease of the gallbladder and bile ducts
- suffer from inflammation of the bowel
- suffer from diseases of the adrenal glands
- suffer from pancreatitis (inflammation of the pancreas, which causes severe pain in the abdomen and back)
- 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 a severe headache or feel sick as this may indicate that the pressure in your skull is increased (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 weak 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.

If you are going to have an operation, please tell the doctor at the hospital that you are taking this medicine.

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 10mg/ml Solution:
- tranquillizers and sleeping tablets
- anxiolytics
- 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
- medicines to treat high blood pressure
- quinidine (a medicine to treat a fast heart beat)
- clonidine (a medicine for stomach ulcers, indigestion or hearburn)
- antihypertensive medicines (such as ketoconazole)
- antibiotics (such as erythromycin)
- monoamine oxidase inhibitors (MAOIs) (used in depression) — wait at least 2 weeks after stopping MAOIs before using this medicine.

Taking Oxycodone 10mg/ml Solution 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 taking this medicine.

Pregnancy and breastfeeding
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 10mg/ml Solution may cause drowsiness and reduced alertness, do not drive or operate machinery while taking this medicine.

Important information about some of the ingredients in Oxycodone 10mg/ml Solution
A total daily dose of 400mg of this medicine contains approximately 34mg sodium. To be taken into consideration in patients on a controlled sodium diet.

This medicine contains sugar yellow (E101), which may cause allergic reactions.

2. Before you take Oxycodone 10mg/ml Solution

Your doctor will determine the dose you require.

Adults (over 18 years of age)
The usual starting dose is 5mg every four to six hours. However, your doctor will prescribe the dose required to treat your pain. If you find that you are still in pain whilst taking this medicine discuss this with your doctor.

Patients with kidney and liver disease
The dosage should follow a conservative approach. The usual starting dose is 2.5mg every 6 hours.
PAR Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution

Do not exceed the dose recommended by your doctor.
Not to be used in patients under 18 years of age.
You must only take this medicine by mouth. This medicine should never be injected or used as a nasal spray. Severe side effects may occur.
If you take more Oxycodone 10mg/ml Solution than you should:
Call your doctor or hospital immediately. People who have taken an overdose may feel very sleepy, sick or dizzy. They may also have breathing difficulties leading to unconsciousness or even death. They may need emergency treatment from hospital. Make sure you have this leaflet and any remaining medicine you have to show the doctor.
If you forget to take Oxycodone 10mg/ml Solution:
If you miss a dose you should take the next dose as soon as you remember, then carry on as before. Do not take two doses within four hours. Do not take a double dose to make up for a forgotten dose.
If you stop taking Oxycodone 10mg/ml Solution:
Patients can become tolerant to the effects of oxycodone if they use it over a long time or if they are already using oxycodone and may require progressively higher doses in order to maintain pain control.
Prolonged use of this medicine may lead to dependence and if treatment is stopped abruptly you may experience withdrawal symptoms. These symptoms include restlessness, running nose and eyes, yawning, sweating, chills, muscle pain, abdominal pain, diarrhea, and prolonged dilatation of the pupils. You should not suddenly stop taking this medicine unless your doctor tells you to. If you want to stop taking this medicine, discuss this with your doctor first. They will tell you to stop treatment gradually over some time in order to prevent unpleasant symptoms.

4 Possible side effects
Like all medicines, Oxycodone 10mg/ml Solution 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, problems swallowing, anaphylaxis (severe allergy),

Side effects that have been reported with Oxycodone 10mg/ml Solution are:

Common (occurs in more than 1 in 100 patients):
- sleepiness
- constipation
- vomiting
- abnormal thinking
- weakness
- loss of appetite
- dry mouth
- rash
- problems passing water
- chills
- anxiety
- problems sleeping
- muscle fatigue
- nervousness
- low blood pressure
- dizziness
- nausea
- irritability
- confusion
- drowsiness
- injection site pain
- dryness
- constipation
- insomnia
- memory loss
- hallucinations
- rapid breathing
- flushing
- speech problems
- increased muscle tone

Uncommon (occurs in fewer than 1 in 100 patients):
- hormone disturbances
- weight change
- decreased sex drive
- hallucinations
- memory loss
- injection site pain
- anaphylaxis
- dehydration
- swelling of the legs

5 How to store Oxycodone 10mg/ml Solution
Keep out of the reach and sight of children.
- Do not store above 25°C.
- Store in the original package in order to protect from light.
- Do not use after the expiry date (shown as Exp. on the packaging). The expiry date refers to the last day of the month, your doctor or nurse will check for this.
- Once opened this medicine must be used within one month.
- Consult a pharmacist if signs of deterioration of the product are observed.

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

6 Further information
What is this medicine?
Oxycodone 10mg/ml Solution contains:
The active ingredient is oxycodone hydrochloride. Each 1ml contains oxycodone hydrochloride 10mg (equivalent to 9mg oxycodone base). The other ingredients are: citric acid monohydrate, sodium citrate, sodium benzoate, sodium saccharin, sunset yellow (E110) and purified water.

What is Oxycodone 10mg/ml Solution Solution looks like and the contents of the pack:
This medicine is a clear orange solution. Each bottle contains 125ml of solution. An oral syringe is also supplied.

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: Oxycodone Hydrochloride 10mg/ml Oral Solution
Maris: Oxycodone Hydrochloride 10mg/ml Oral Solution

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call 24800 196 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 Hydrochloride 10mg/ml Oral Solution</td>
<td>PL 26831/0459</td>
</tr>
</tbody>
</table>

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

Leaflet Prepared: March 2011

Module 4
Labelling

Label

Each 5ml of solution contains 5mg of oxycodone hydrochloride.

Dose: as directed by the doctor.

Read the package leaflet before use.

Contains sodium.

Read the package leaflet for further information.

For oral use.

Do not store above 25°C.

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

Once opened the product should be used within 1 month.

Keep out of the reach and sight of children.

PL 29831/0458 MA 154/06901

Oxycodone Hydrochloride

5mg/5ml

Oral Solution
(sugar free)

250ml
PAR Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution UK/H/2780/001-2/DC

Carton

Each 5ml of solution contains 5mg of oxycodone hydrochloride.

Dose: As directed by the doctor.

Read the package leaflet before use.

Carton contents:

- Oral Solution (sugar free)
- For oral use

Marketing Authorisation Holder:

Weleda UK Ltd, Ash Road, Reading, Berkshire. RG1 3UF, UK

Ph. 20314565

W.A. 154/16901
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
On 17 April 2011, Malta and the UK agreed to grant Marketing Authorisations (MAs) to Wockhardt UK Ltd for the medicinal products Oxycodone Hydrochloride 5mg/5ml Oral Solution and Oxycodone Hydrochloride 10mg/ml Oral Solution. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/2780/001-002/DC). After the national phase, MAs were granted in the UK on 25 May 2011 (PL 29831/0458 and PL 29831/0259).

These applications were made under Article 10.1 of Directive 2001/83/EC for Oxycodone Hydrochloride 5mg/5ml Oral Solution and Oxycodone Hydrochloride 10mg/ml Oral Solution, containing the known active substance oxycodone hydrochloride. The reference medicinal products for these applications are OxyNorm® liquid 5mg/5ml (PL 16950/0003) and OxyNorm® concentrate 10mg/ml oral solution (PL 16950/0004), both licensed on 9 December 1999 to Napp Pharmaceuticals Limited.

Oxycodone is an opioid analgesic with similarities to morphine and other opioids. Oxycodone Hydrochloride Oral Solution has been primarily prepared for use in the treatment of moderate to severe pain in patients with cancer and post-operative pain and also for the treatment of severe pain requiring the use of a strong opioid; it would also be effective if used to relieve diarrhoea or intractable coughing.

No new preclinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the application was for a generic version of product that has been licensed for over 10 years. A bioequivalence study is not necessary to support these applications for an oral solution.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. 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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community 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 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.

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.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Oxycodone Hydrochloride 5 mg/5 ml Oral Solution  
Oxycodone Hydrochloride 10 mg/ml Oral Solution |
<table>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Oxycodone Hydrochloride</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code) | Natural opium alkaloids  
N02A A05                                                                 | |
| Pharmaceutical form and strength(s)           | Oral Solution,  
1 mg/ml (5 mg/5 ml) & 10 mg/ml                                                               |
| Reference numbers for the Decentralised Procedure | UK/H/2780/001/DC  
UK/H/2780/002/DC                                                                 |
| Reference Member State                        | United Kingdom                                                                                  |
| Member States concerned                      | Malta                                                                                           |
| Marketing Authorisation Number(s)            | PL 29831/0458  
PL 29831/0459                                                                 |
| 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

DRUG SUBSTANCE

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

Structure:

Molecular formula: $\text{C}_{18}\text{H}_{22}\text{ClNO}_4$
Molecular weight: 351.9

General Properties

Description: 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 Pharmacopeia (Ph. Eur.) monograph.

Manufacture

All aspects of the manufacture and control of the active substance oxycodone hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

The active substance is stored in appropriate packaging. The primary packaging is a low density polyethylene bag inside either an aluminium tin, a polypropylene drum or a high-density polyethylene drum. A re-test period of 5 years has been applied when stored in the stated container closure system.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate, sodium citrate, sodium benzoate, sodium saccharin, purified water, hypromellose (methocel-E15-premium LV) 5mg/5ml strength only and sunset yellow (E110) 10mg/ml strength only. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients used comply with their respective European Pharmacoeial monograph with the exception of sunset yellow (E110) which is controlled to an in-house specification. Satisfactory Certificates of Analyses for each excipient have been provided. 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. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical Development

The aim of the pharmaceutical development programme was to produce robust, reproducible products that could be considered generic medicinal products of OxyNorm® liquid 5mg/5ml,
oral solution and OxyNorm® concentrate 10mg/ml oral solution (Napp Pharmaceutical Limited). Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug product have been compared with the reference product. These data demonstrate that the proposed product can be considered a generic medicinal products OxyNorm® liquid 5mg/5ml, oral solution and OxyNorm® concentrate 10mg/ml oral solution (Napp Pharmaceutical Limited).

Impurity Profiles
Comparative impurity data were provided for the test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

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

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from 2 pilot-scales batches were provided.

Finished Product Specification
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 adequately validated, as appropriate. Batch data are provided for 2 pilot-scale batches of strength of the product, which demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
Oxycodone Hydrochloride 5mg/5ml Oral Solution is licensed for marketing in 250 ml amber soda glass (type III) bottles, fitted with 28 mm white child resistant tamper evident caps with expanded polyethylene (EPE) liners, contained in outer cardboard cartons packaged with the Patient Information Leaflet (PIL).

Oxycodone Hydrochloride 10mg/ml Oral Solution is licensed for marketing in 125 ml amber soda glass (type III) bottles, fitted with 28 mm white child resistant tamper evident caps with expanded polyethylene (EPE) liners, contained in outer cardboard cartons packaged with the PIL. In addition a 3ml dosing dispenser and a bottle adapter will be supplied with each pack.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. The glass bottles comply with Ph Eur requirements and is suitable for contact with oral solution products; the cap comply with child resistant packaging legislation.

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 18 months has been set, when the bottle is unopened, which is satisfactory. Storage instructions are ‘Do not store above 25°C’ and ‘Store in original package in order to protect from light.’
An ‘in-use’ product stability study was carried out on Oxycodone Hydrochloride Oral Solution to establish the time period over which the product could be used after the bottle has been opened. The results showed that at all time points all of the specification requirements were met. The conclusion being that this data supports a 1 month ‘in-use’ shelf life.

**Bioequivalence Study**
The products are aqueous oral solutions at the time of administration and contain the same concentration of the active substance as the reference product, OxyNorm® Liquid; bioequivalence studies from a quality perspective can be waived.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that is contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Conclusion**
The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to perform a bioequivalence study.

There are no objections to the approval of Oxycodone Hydrochloride 5mg/5ml Oral Solution and Oxycodone 10mg/ml Oral Solution from a pharmaceutical point of view.

**III.2 PRE-CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of oxycodone hydrochloride are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

The SmPC is satisfactory from a pre-clinical viewpoint and is consistent with that for the reference product.

There are no objections to approval of Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution from a pre-clinical point of view.
III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution are generic versions of OxyNorm® liquid 5mg/5ml oral solution and OxyNorm® concentrate 10mg/ml oral solution. The use of the reference products is well-established in the UK. Both the reference products and the test products contain the same quantitative and qualitative composition of the active ingredient, oxycodone hydrochloride.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous oral solution containing the same active substance, in the same concentration as the currently authorised product according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and applicant has submitted none which is satisfactory.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
No new safety data have been submitted or required for these generic applications. As oxycodone hydrochloride is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to approval of Oxycodone Hydrochloride 5mg/5ml Oral Solution and Oxycodone Hydrochloride 10mg/ml Oral Solution from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution 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.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s products Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution have been demonstrated to be generic versions of the reference products OxyNorm® liquid 5mg/5ml oral solution and OxyNorm® concentrate 10mg/ml oral solution (Napp Pharmaceuticals Limited, UK).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs and PILs are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet 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 package leaflet 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.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s products Oxycodone Hydrochloride 5mg/5ml and 10mg/ml Oral Solution and the reference products OxyNorm® liquid 5mg/5ml oral solution and OxyNorm® concentrate 10mg/ml oral solution (Napp Pharmaceuticals Limited, UK), are interchangeable. Extensive clinical experience with oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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