

Oxeltra 5mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 5mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4.5mg of oxycodone as 5mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is blue, round, biconvex, marked OX 5 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.
Uncommon: dry skin, exfoliative dermatitis
Rare: urticaria.

Renal and urinary disorders:
Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:
Uncommon: erectile dysfunction, hypogonadism
Frequency not known: amenorrhoea.

General disorders and administration site conditions:
Common: asthenia, fatigue
Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia
Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

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

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydroxypropyl methylcellulose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Talc (E553b)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C.

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 28 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd

Ash Road North

Wrexham

LL13 9UF

UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0630

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 10mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 10mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 9mg of oxycodone as 10mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is white, round, biconvex, marked OX 10 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to

mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis
Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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 circulatory 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdose should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

In- vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these

findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Polysorbate (E433)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C.

Bottle container: Do not store above 25°C.

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0631

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 15mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 15mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 13.5mg of oxycodone as 15mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is grey, round, biconvex, marked OX 15 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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 circulatory 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdose should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

In- vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these

findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Talc (E553b)
- Iron oxide black (E172)
- Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0632

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 20mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 20mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 18mg of oxycodone as 20mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is pink, round, biconvex, marked OX 20 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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 circulatory 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdose should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

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

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Talc (E553b)
- Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0633

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 30mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 30mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 27mg of oxycodone as 30mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is brown, round, biconvex, marked OX 30 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.
Uncommon: dry skin, exfoliative dermatitis
Rare: urticaria.

Renal and urinary disorders:
Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:
Uncommon: erectile dysfunction, hypogonadism
Frequency not known: amenorrhoea.

General disorders and administration site conditions:
Common: asthenia, fatigue
Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia
Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store..

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

In- vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these

findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Macrogol (E1521)
- Talc (E553b)
- Iron oxide red (E172)
- Iron oxide black (E172)
- Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0634

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 40mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 40mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 36mg of oxycodone as 40mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is yellow, round, biconvex, marked OX 40 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets

leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%;AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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 circulatory 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdose should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

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

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

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Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

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Povidone
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Film Coating contains:

- Polyvinyl alcohol (E1203)
- Titanium dioxide (E171)
- Macrogol (E1521)
- Talc (E553b)
- Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C.

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0635

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 60mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 60mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 54mg of oxycodone as 60mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is red, round, biconvex, marked OX 60 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

Oxeltra 60 mg tablets should not be used in patients not previously exposed to opioids. This tablet strength may cause fatal respiratory depression when administered to opioid naïve patients.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%; AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia.

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased.

Uncommon: respiratory depression, hiccups.

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis.

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic.

Frequency not known: cholestasis.

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis.

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm.

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism..

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia.

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

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

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Macrogol (E1521)
- Talc (E553b)
- Iron oxide red (E172)
- Carmine (E120)
- Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C.

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0636

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

14/11/2014

10. DATE OF REVISION OF THE TEXT

28/08/2018

Oxeltra 80mg Prolonged-Release Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxeltra 80mg Prolonged-Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 72mg of oxycodone as 80mg of oxycodone hydrochloride.

Excipient with known effect

Contains lactose monohydrate (see section 4.4).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Each film-coated tablet is green, round, biconvex, marked OX 80 on one side.

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

Method of administration

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed.

Posology

Elderly and adults over 18 years:

Oxeltra tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

Oxeltra is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of Oxeltra tablets using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of Oxeltra tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before Oxeltra 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 Oxeltra tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients

A dose adjustment is not usually necessary in elderly patients. 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.

Children under 18 years:

Oxeltra should not be used in patients under 18 years of age.

Patients with renal or hepatic impairment:

The plasma concentration in this population may be increased. The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

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.

Duration of treatment:

Oxycodone should not be used for longer than necessary.

Discontinuation of treatment:

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

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1. Oxycodone must not be used in any situation where opioids are contraindicated: severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency, alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Oxeltra tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, Oxeltra tablets should be discontinued immediately.

Oxeltra is not recommended for pre-operative use or within the first 12-24 hours post-operatively.

Oxeltra 80 mg tablets should not be used in patients not previously exposed to opioids. This tablet strength may cause fatal respiratory depression when administered to opioid naïve patients.

As with all opioid preparations, Oxeltra tablets 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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive Oxeltra tablets for 12 hours prior to the intervention. If further treatment with Oxeltra tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this tablet 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.

Hyperalgesia that will not respond to a further dose increase of oxycodone may occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. Oxeltra tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Oxeltra tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9).

Concomitant use of alcohol and Oxeltra may increase the undesirable effects of Oxeltra; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

Oxeltra 5 mg tablets contain lactose monohydrate (31.60 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Empty matrix (tablets) may be seen in the stools.

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 manifest from these hormonal changes.

4.5 Interaction with other medicinal products and other forms of interaction

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

Drugs which affect the CNS include, but are not limited to: alcohol, tranquillisers, anaesthetics, hypnotics, anti-depressants, non-benzodiazepine sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

MAO inhibitors are known to interact with narcotic analgesics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of Oxeltra; concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly. Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).
- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).
- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).
- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John's Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St John's Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).
- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concurrent administration of quinidine resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and t_{1/2} elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%; AUC by 85%, and t_{1/2} elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oxeltra tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxeltra tablets should, therefore, not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the 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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

4.8 Undesirable effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see Section 4.4). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $<1/10$
Uncommon	$\geq 1/1,000$ to $<1/100$
Rare	$\geq 1/10,000$ to $<1/1,000$
Very rare	$<1/10,000$
Frequency not known	Cannot be estimated from the available data

Immune system disorders:

Uncommon: hypersensitivity.

Frequency not known: anaphylactic reaction, anaphylactoid reaction.

Metabolism and nutrition disorders:

Common: decreased appetite.

Uncommon: dehydration.

Psychiatric disorders:

Common: anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking, abnormal dreams

Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4), disorientation, mood altered, restlessness, dysphoria

Frequency not known: aggression.

Nervous system disorders:

Very common: somnolence, dizziness, headache.

Common: tremor, lethargy, sedation

Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia, hypotonia

Frequency not known: hyperalgesia.

Eye disorders:

Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:

Uncommon: vertigo.

Cardiac disorders:

Uncommon: palpitations (in the context of withdrawal syndrome), supraventricular tachycardia

Vascular disorders:

Uncommon: vasodilatation, facial flushing

Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea, bronchospasm, cough decreased

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders:

Very common: constipation, nausea, vomiting.

Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.

Uncommon: dysphagia, flatulence, eructation, ileus, gastritis

Frequency not known: dental caries.

Hepato-biliary disorders:

Uncommon: increased hepatic enzymes, biliary colic

Frequency not known: cholestasis

Skin and subcutaneous tissue disorders:

Very common: pruritus.

Common: rash, hyperhidrosis.

Uncommon: dry skin, exfoliative dermatitis

Rare: urticaria.

Renal and urinary disorders:

Uncommon: urinary retention, ureteral spasm

Reproductive system and breast disorders:

Uncommon: erectile dysfunction, hypogonadism

Frequency not known: amenorrhoea.

General disorders and administration site conditions:

Common: asthenia, fatigue

Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia

Frequency not known: drug withdrawal syndrome neonatal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema 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 oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

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 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.

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. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.
- Oxeltra tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly. Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: NO2A AO5

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate 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.

Endocrine system

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.

Other pharmacological effects

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

Clinical studies

The efficacy of oxycodone tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of oxycodone tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

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 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from oxycodone tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of oxycodone tablets is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from oxycodone tablets is independent of pH.

Oxycodone tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from Oxycodone tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of Oxeltra tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from oxycodone tablets.

Elderly

The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d.

Carcinogenicity

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.

Mutagenicity

The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hydroxypropyl methylcellulose (E464)
Povidone
Stearic acid
Magnesium stearate
Silica colloidal, anhydrous

Film Coating contains:

- Polyvinyl alcohol (E1203)
- Macrogol (E1521)
- Talc (E553b)
- Titanium dioxide (E171)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

In-use shelf life: 6 months (bottle container)

6.4 Special precautions for storage

Blister packs: Do not store above 25°C.

Bottle container: Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil containing 56 tablets. HPDE containers with LDPE cap containing 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0637

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

28/08/2018

