SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Longtec 120 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 108 mg of oxycodone as 120 mg of oxycodone hydrochloride.

Excipient with known effect
Contains lactose monohydrate
For the full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Purple, round, convex tablets marked OC on one side and 120 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of moderate to severe pain in patients with cancer. For the treatment of severe pain requiring the use of a strong opioid.

4.2 Posology and method of administration

Adults over 18 years:
Longtec 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.

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with oxycodone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Longtec tablets are not intended for use as a prn analgesic.

Generally, the lowest effective dose for analgesia should be selected. Increasing severity of pain will require an increased dosage of ***Longtec*** tablets, using the different 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 in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of ***Longtec*** 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.

Conversion from oral morphine:
Patients receiving oral morphine before ***Longtec*** 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 ***Longtec*** tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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

Elderly 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.

Paediatric population
Longtec 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..

Method of administration
Longtec tablets are for oral use.
Longtec tablets must be swallowed whole and not broken, chewed or crushed.

Treatment goals and discontinuation

Before initiating treatment with ***Longtec*** tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Oxycodone should not be used for longer than necessary.

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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4 CLINICAL PARTICULARS

4.4 Special warnings and precautions for use

Caution must be exercised when administering oxycodone to the debilitated elderly, patients with severely impaired pulmonary function, patients with impaired hepatic or renal function, patients with myxoedema, 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, intracranial lesions, head injury (due to risk of increased intracranial pressure), reduced level of consciousness of uncertain origin, sleep apnoea or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors (see section 4.5).

The primary risk of opioid excess is respiratory depression.

Sleep related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing central sleep apnoea (see section 4.8).

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

If a decision is made to prescribe oxycodone concomitantly with sedative medicines, 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 patient 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 caregivers to be aware of these symptoms (see section 4.5).

Longtec tablets must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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

Longtec tablets are not recommended for pre-operative use or within the first 12-24 hours post-operatively.

Prolonged release opioids should not be used for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

As with all opioid preparations, oxycodone products 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 ***Longtec*** tablets for 12 hours prior to the intervention. If further treatment with ***Longtec*** 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. See section 4.2 for additional information on treatment goals and discontinuation.

Tolerance, Dependence and Opioid Use Disorder

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Repeated use of ***Longtec*** tablets may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of ***Longtec*** tablets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with ***Longtec*** tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). The prescriber should conduct a review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially

experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with oxycodone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the Sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** tablets leads to a

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

Concomitant use of alcohol and ***Longtec*** may increase the undesirable effects of ***Longtec***; 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.

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

Opioids such as oxycodone hydrochloride 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 opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
Drugs which affect the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, anaesthetics, muscle relaxants, antihypertensives and alcohol.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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). Co-administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use should be avoided.

Alcohol may enhance the pharmacodynamic effects of ***Longtec***; 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. Oxycodone doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azole-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, carbamazepine, 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 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 $t_{½}$ elim. by 14%. Also, an increase in noroxycodone level was observed, (C_{max} by 50%; AUC by 85%, and $t_{½}$ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Longtec tablets are not recommended for use in pregnancy nor during labour. There are limited data from the use of oxycodone in pregnant women. Regular use in pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding
Administration to nursing women is not recommended as oxycodone may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

No human data on the effect of oxycodone on fertility are available. In rats there was no effect on mating or fertility with oxycodone treatment (see section 5.3).

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 you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - 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.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

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	≥ 1/10
Common	≥ 1/100 to <1/10
Uncommon	≥ 1/1,000 to <1/100
Rare	≥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, disorientation, mood altered, restlessness, dysphoria.
Frequency not known: aggression, drug dependence (see section 4.4).

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.
Not known: central sleep apnoea syndrome.

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, spasm of sphincter of oddi.

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: malaise, oedema, peripheral oedema, thirst, pyrexia, chills.
Frequency not known: drug withdrawal syndrome neonatal, opioid tolerance, opioid withdrawal syndrome.

Opioid Tolerance and Opioid Withdrawal Syndrome
The frequency of opioid tolerance and the frequency of opioid withdrawal syndrome cannot be estimated from available evidence (e.g. clinical trials, spontaneous reporting, and the medical literature) and therefore is classified as "not known" (see section 4.8). 'Not known' should not be interpreted as an indication of the rarity of the occurrence of opioid tolerance and opioid withdrawal syndrome, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

The frequency of "not known" above regarding opioid tolerance and opioid withdrawal syndrome reflects the high variability of risk depending upon: definition of tolerance and withdrawal syndrome; dose and duration of treatment; and assessment and monitoring methods (specific to withdrawal syndrome). As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), tolerance and withdrawal syndrome (see section 4.4 on monitoring and risk reduction interventions).

Drug dependence
The frequency above regarding drug dependence reflects the current evidence, including cumulative data from clinical trials and additional post marketing sources, and indicates that the risk of drug dependence with opioids is highly

variable depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. 'Not known' should not be interpreted as an indication of the rarity of occurrence of drug dependence, but a reflection of the limitations in available evidence that do not support a precise estimate of frequency.

Repeated use of ***Longtec*** tablets may lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage and duration of opioid treatment (see section 4.4 for monitoring and risk reduction interventions).

The frequency of 'not known' in the above table regarding drug dependence reflects the high variability of risk depending upon: definition of drug dependence; duration of treatment; dose; individual patient risk factors; and clinical settings. As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), addiction, abuse, and misuse, as well as opioid use disorder and problematic opioid use. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone. Addiction can occur at recommended doses, and if the drug is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The frequency of drug dependence also increases with longer term use or higher doses of oxycodone. See section 4.4 on monitoring and risk reduction interventions.

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.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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 an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.

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

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

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

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.

- ***Longtec*** tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdosage should be modified accordingly. Gastric contents may therefore need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids

ATC code: N02A A05

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

Gastrointestinal System
Opioids may induce spasm of the sphincter of Oddi.

Endocrine system
See section 4.4

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 ***Longtec*** 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 ***Longtec*** 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

Absorption
The release of oxycodone from ***Longtec*** 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.

Release of oxycodone from ***Longtec*** tablets is independent of pH.

Longtec 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 ***Longtec*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

All strengths of ***Longtec*** tablets are bioequivalent in terms of both rate and extent of absorption.

Distribution
Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein.

Metabolism
Oxycodone is metabolised in the liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone is a weak mu opioid agonist. Noroxymorphone is a potent mu opioid agonist; however, it does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu opioid agonist but is present at very low concentrations following oxycodone administration. None of these metabolites are thought to contribute significantly to the analgesic effect of oxycodone.

Elimination
The mean apparent elimination half-life of ***Longtec*** is 4.5 hours, which leads to steady-state being achieved in about one day. The active drug and its metabolites are excreted in urine.

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 $t_{½}$ 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 $t_{½}$ elimination for oxycodone increased by 2.3 hours.

5.3 Preclinical safety data

Reproductive and Development Toxicology
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. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual foetuses were analysed.

However, when the same data were analysed using litters as opposed to individual foetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the foetal findings may have been a secondary consequence of severe maternal toxicity.

In a prenatal and postnatal development study in rats, maternal body weight and food intake parameters were reduced for doses ≥ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Genotoxicity
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.

Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an *in-vivo* micronucleus assay in the mouse. Oxycodone produced a positive response in the *in-vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 μg/mL. Two *in-vitro* chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at other time points or at 48 hour after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

Carcinogenicity
Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Povidone
Ammoniomethacrylate co-polymer
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film coat
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80 (E433)
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

PVC blister packs with aluminium foil backing (containing 28, 56 or 112* tablets).
* Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Qdem Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 40431/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

18/03/2025