Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zomestine 10 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg oxycodone hydrochloride equivalent to 9.0 mg oxycodone.
Excipient with known effect: The prolonged-release tablets contain a maximum of 30 mg sucrose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Pink, oblong, 10.3 – 10.4 mm in length and 4.7 – 4.8 mm in width, biconvex, prolonged-release tablets with break scores on both sides.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe pain, which can be adequately managed only with opioid analgesics.

This medicine is indicated in adults and adolescents above 12 years of age.

4.2 Posology and method of administration

The dosage depends on the intensity of pain and the patient's individual susceptibility to the treatment. For doses not realisable/practicable with this medicinal product, other strengths and medicinal products are available.
This medicine is indicated in adults and adolescents above 12 years of age.

The following general dosage recommendations apply:

Adults and adolescents (> 12 years)
Dose titration and adjustment
In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of adverse reactions.
Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.
Zomestine is not intended for use as a prn (pro re nata or as needed) analgesic.

According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.
Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Zomestine prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.
Some patients who take Zomestine prolonged-release tablets following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Zomestine prolonged-release tablets are not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Zomestine prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Zomestine prolonged-release tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.
Following a dose increase from 10 mg to 20 mg taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individually balancing efficacy with the tolerance and risk of undesirable effects.

Method of administration
For oral use.
Zomestine prolonged-release tablets should be taken twice daily based on a fixed schedule at the dosage determined.
The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid.

Zomestine 10 mg prolonged-release tablets should be swallowed either whole or broken up (the tablet can only be broken in two when using the score line), not chewed or crushed.
The administration of chewed or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.4 and 4.9).

Zomestine should not be taken with alcoholic beverages (see section 4.4.)

Paediatric population
Zomestine prolonged-release tablets are not recommended for children under 12 years of age.

Patients older than 65 years
In older patients without clinical manifestation of impaired liver and/or kidney function usually do not require dose adjustments. However, in general, the initial dose in frail opioid-naive geriatric patients is 5 mg oxycodone hydrochloride given at intervals of 12 hours.

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
Zomestine prolonged-release tablets should not be taken longer than necessary. If long-term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued.

Discontinuation of treatment
If opioid therapy is no longer indicated it may be advisable to reduce the daily dose gradually in order to prevent symptoms of a withdrawal syndrome.

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 , elevated carbon dioxide levels in the blood,
● severe chronic obstructive pulmonary disease,
● Cor pulmonale,
● severe bronchial asthma,
● Paralytic ileus,
● acute abdomen, delayed gastric emptying,
● Any situation where opioids are contra-indicated,

● 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 administration of chewed or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (section 4.9)

Zomestine prolonged-release tablets have not been studied in children younger than 12 years of age. The safety and efficacy of the tablets have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

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, patients with impaired hepatic or renal function, patient with myxedema, hypothyroidism, Addison's disease , delirium tremens, pancreatitis, diseases of the biliary tract, hypotension, hypovolaemia, toxic psychosis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, and patients with raised intracranial pressure, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.

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

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

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 Zomestine prolonged-release tablets for 12 hours prior to the intervention. If further treatment with Zomestine prolonged-release tablets is indicated then the dosage should be adjusted to the new post-operative requirement.

Zomestine 80 mg prolonged-release tablets should not be used in patients not previously exposed to opioids. These tablet strength may cause fatal respiratory depression when administered to opioid naïve patients.

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 product 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.

Zomestine prolonged-release tablets 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. Zomestine 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.

Abuse of oral dosage forms by parenteral administration can be expected to result in other serious adverse events, such as local tissue necrosis, infection, increased risk of endocarditis, pulmonary granulomas, and valvular heart injury which may be fatal. The administration of chewed or crushed tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Concomitant use of alcohol and Zomestine prolonged release tablet may increase the undesirable effects of Zomestine prolonged release tablet; concomitant use should be avoided.

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

Concomitant use of Zomestine prolonged release tablet 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 Zomestine prolonged release tablet concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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 caregivers to be aware of these symptoms (see section 4.5).

Anti-Doping Warning
Athletes should be aware that this medicine may cause a positive reaction to “anti-doping tests”.
Use of Zomestine Prolonged-release Tablets as a doping agent may become a health hazard.

4.5 Interaction with other medicinal products and other forms of interactions

Central nervous system depressants & other Opioids
There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, other opioids, muscle relaxants and antihypertensives.

Anticholinergics
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.

Alcohol
Alcohol may enhance the pharmacodynamic effects of Zomestine prolonged release tablet; concomitant use should be avoided.

MAO-inhibitors
MAO-inhibitors are known to interact with narcotic analgesics. MAO-inhibitors causes CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with particular caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

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

CYP3A4 inhibitors

CYP3A4 inhibitors, such as macrolideantibiotics (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), cimetidin 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
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. Therefore 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 qunidine, may cause a reduced clearance of oxycodone that could cause increased plasma concentrations of oxycodone.

Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone Cmax by 11%, AUC by 13%, and t½elim. by 14%. Also an increase in noroxycodone level was observed, (Cmax by 50%; AUC by 85%, and t½elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

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

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.
Pregnancy
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.

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

4.7 Effects on ability to drive and use machines

Zomestine prolonged-release tablets has major influence on ability to drive and use machines. This is particularly likely at the initiation of treatment with Zomestine prolonged-release tablets, after dose increase or product rotation and if Zomestine prolonged release tablets is combined with alcohol or other CNS depressant agents. With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

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:

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 dreams, abnormal thinking.
Uncommon: hallucinations, agitation, altered mood, restlessness, disorientation, dysphoria, euphoric mood, decreased libido, affect lability, drug dependence (see section 4.4).
Frequency unknown: aggression.

Nervous system disorders

Very common: somnolence, dizziness, headache.
Common: tremor, lethargy, sedation.
Uncommon: amnesia, hypertonia, hypoesthesia, speech disorder, convulsions, involuntary muscle contractions, paraesthesia, taste perversion (dysgeusia), syncope.
Frequency unknown: hyperalgesia

Eye disorders
Uncommon: miosis, visual impairment

Ear and labyrinth disorders
Uncommon: Vertigo

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

Vascular disorders
Uncommon: vasodilatation, facial flushing
Rare: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: cough decreased, bronchospasm, dyspnoea

Uncommon: respiratory depression, hiccups

Gastrointestinal disorders

Very common: constipation, nausea, vomiting

Common: dry mouth, abdominal pain, diarrhoea, dyspepsia,
Uncommon: dysphagia, eructation, gastritis, ileus, flatulence.
Frequency not known: dental caries

Hepato-biliary disorders
Uncommon: increased hepatic enzymes, biliary colics
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: drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst, pyrexia, chills.
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517 , Website: www.hpra.ie E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of 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.

Therapy of overdose
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 event of overdosing intravenous administration of an opiate antagonist (e.g. 0.4-2 mg intravenous naloxone for an adult and 0.01mg/kg body weight for children) may be indicated if the patient is in a coma or respiratory depression is present. Administration of single doses must be repeated depending on the clinical situation at intervals of 2 to 3 minutes. 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 overdose. Naloxone should be administered cautiously to patients 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.

Zomestine prolonged-release 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: Analgesics. Opioids. Natural opium alkaloids, ATC-Code: N02AA05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

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

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 Zomestine prolonged-release 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 Zomestine prolonged-release 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.

Absorption
The relative bioavailability of Zomestine prolonged-release tablets is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.
A fat-rich meal before the intake of the tablets does not affect the maximum concentration or the extent of absorption of oxycodone.
The tablets must not be crushed or chewed as this leads to rapid oxycodone release due to the damage of the prolonged-release properties.

Distribution
The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration. In steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg; plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 l/min. The elimination half-life of oxycodone from prolonged-release tablets is 4-5 hours with steady state values being achieved after a mean of 1 day.

Metabolism
The main metabolic pathways of oxycodone are N-demethylation (CYP3A4) to inactive noroxycodone and O-demethylation (CYP2D6) to activeoxymorphone. Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs (see section 4.4).

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for ketoreduction and glucuronidation pathways in oxycodone metabolism have not been established.

CYP2D6 genetic polymorphism could affect oxycodone pharmacodynamics. Several case reports describe reduced analgesic effect of oxycodone in CYP2D6 poor metabolizers (see Samer CF *et al*). Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. (Br J Pharmacol. 2010. 160:919-930, and references therein).

Elimination
Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk.

Linearity/non-linearity
The 5, 10, 20, 40 and 80 mg prolonged-release tablets are bioequivalent in a dose proportional manner with regard to the amount of active substance absorbed as well as comparable with regard to the rate of absorption.

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 t½ 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

Oyxcodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices.
In a study of peri- and postnatal development 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.

Carcinogenicity
Long-term carcinogenicity studies were not performed.
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
These 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 microgram/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Sugar spheres (contains sucrose, maize starch, starch hydrolysates and colour additives)
Hypromellose
Talc
Ethylcellulose
Hydroxypropylcellulose
Propylene glycol
Carmellose sodium

Microcrystalline cellulose
Magnesium stearate
Silica, colloidal anhydrous
Tablet coating:
Zomestine 10mg prolonged-release tablets
Titanium dioxide (E171)
Macrogol 3350
Talc
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child resistant PVC/PE/PVDC-aluminium blisters consisting of a white opaque PVC/PE/PVDC laminated foil and an aluminium foil.
HDPE bottles with child-resistant PP twist-off caps.

Pack sizes:
10, 14, 20, 28, 30, 50, 56, 60, 98, 100 and 120 prolonged-release tablets in blister.
10, 20, 30, 50, 100 prolonged-release tablets in HDPE bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/169/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 12th October 2012

Date of last renewal: 31st December 2013

10 DATE OF REVISION OF THE TEXT