1. **NAME OF THE MEDICINAL PRODUCT**

   *OxyNorm Dispera* 5, 10, 20 mg orodispersible tablets

2. **QUALITATIVE AND QUANTATIVE COMPOSITION**

   Each tablet contains 4.5 mg, 9 or 18 mg of oxycodone as 5, 10, or 20 mg of oxycodone hydrochloride.

   Excipients with known effect:
   Each 5 mg tablet contains 2.7 mg of aspartame (E 951) and 14.2 mg of sucrose.
   Each 10 mg tablet contains 5.4 mg of aspartame (E 951) and 28.4 mg of sucrose.
   Each 20 mg tablet contains 10.8 mg of aspartame (E 951) and 56.8 mg of sucrose.

   For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

   Orodispersible tablet

   5 mg: White to off-white round, flat, bevelled edged tablets of approximately 8 mm in diameter marked O on one side and 5 on the other.
   10 mg: White to off-white round, flat, bevelled edged tablets of approximately 9 mm in diameter marked O on one side and 10 on the other.
   20 mg: White to off-white round, flat, bevelled edged tablets of approximately 12 mm in diameter marked O on one side and 20 on the other.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

   For the treatment of severe pain. *OxyNorm Dispera* are indicated in adults aged 20 years and over.

4.2. **Posology and method of administration**

   **Posology**
   Prescribers should consider concomitant treatment with antiemetics and laxatives for the prevention of nausea, vomiting and constipation.

   **Adults:**
   *OxyNorm Dispera* should be taken at 4-6 hourly intervals. The dosage is dependent on the severity of the pain and the patient’s previous history of analgesic requirements, the patient’s body weight, and sex (higher plasma concentrations are produced in females).

   The usual starting dose for debilitated elderly patients, opioid naïve patients or patients presenting with severe pain uncontrolled with weaker opioids is 5 mg 4-6 hourly. The dose should then be carefully titrated, every day if necessary, to achieve optimal pain relief. Where possible, increases should be made in 25-50% increments. The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosage interval.
**Conversion from oral morphine:**
Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of **OxyNorm Dispersa** 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.

**Non-malignant pain:**
Treatment with oxycodone should be short and intermittent to minimise the risk of dependence. The need for continued treatment should be assessed at regular intervals. Patients should not usually require more than 160 mg per day. For the long-term treatment of severe pain prolonged release formulations of oxycodone are available.

**Cancer-related pain:**
Patients should be titrated up to a dose which achieves pain relief unless unmanageable adverse drug reactions prevent this.

**Patients with renal or hepatic impairment:**
Unlike morphine preparations, the administration of oxycodone does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function. 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.

**Other at-risk patients**
Other at-risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve. Dose titration should be performed in accordance with the individual clinical situation.

**Paediatric population and adults under 20 years of age:**
Not recommended.

**Method of administration**
**OxyNorm Dispersa** orodispersible tablets are for oral use.

The tablet is to be placed in the mouth where it should be allowed to disperse rapidly before being swallowed.

**Missed dose:**
If a patient forgets to take a dose, advise them to take a dose as soon as they remember, then go on as before. They must not take two doses within 4 hours. They must not take a double dose to make up for forgotten orodispersible tablets.

**Duration of treatment:**
Oxycodone should not be used 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:**
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, elevated carbon dioxide levels in the blood, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, severe bronchial asthma, cor pulmonale, known sensitivity to morphine or other opioids.

### 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 myxoedema, hypothyroidism, Addison’s disease, toxic psychosis, adrenocortical insufficiency, prostate hypertrophy, head injury (due to the risk of raised intracranial pressure), convulsive disorders, delirium tremens, disorders of consciousness, hypotension, hypovolaemia. Use with caution in opioid dependent patients, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, chronic obstructive airways disease, reduced respiratory reserve, alcoholism or patients taking benzodiazepines, other CNS depressants (including alcohol) or MAO inhibitors. In patients in whom caution is required, a reduction in dosage may be advisable.

**Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:**
Concomitant use of opioids, including 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.

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).

**OxyNorm Dispersa** should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, **OxyNorm Dispersa** should be discontinued immediately (see section 4.3).

**OxyNorm Dispersa** should be used with caution pre-operatively and within the first 12-24 hours post-operatively

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

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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. There may also be cross-tolerance with other opioids. 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. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhea, tremor, hyperhidrosis, anxiety, agitation, irritability, chills, hot flushes, piloerection, joint pain, diaphoresis, abdominal cramps, diarrhoea, convulsions and insomnia.

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 opioid agonists and 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. OxyNorm Dispersa should be used with particular care in patients with a history of alcohol and drug abuse.

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

It should be emphasised that patients, once titrated to an effective dose of a certain opioid, should not be changed to other analgesic preparations without clinical assessment and careful titration as necessary. Otherwise, a continuous analgesic action is not ensured.

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

OxyNorm Dispersa contains a source of phenylalanine which may be harmful to patients with phenylketonuria.

Patients with rare hereditary problems of fructose intolerance glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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. Interactions 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: alcohol, phenothiazines, antidepressants, anaesthetics, hypnotics, non-benzodiazepine sedatives, muscle relaxants, other opioids, neuroleptic drugs, antihypertensives and SSRIs. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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, antiemetics, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects such as constipation, dry mouth or micturition disorders. Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

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

Alcohol may enhance the pharmacodynamic effects of Oxynorm Dispersa, 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), 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 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.

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account.

Clinically relevant changes in International Normalized Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-administered with oxycodone hydrochloride.

There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other drugs.

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.

Oxycodone penetrates the placenta. Oxycodone should not be used during pregnancy and labour due to impaired uterine contractility and the risk of neonatal respiratory depression.

For animals studies see section 5.3.

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.

Fertility
Non-clinical toxicology studies in rats have not shown any effects upon fertility (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. If affected, patients should not drive or operate machinery.

4.8. Undesirable effects

The most commonly reported adverse reactions are nausea and constipation, both occurring in approximately 25 to 30% of patients. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation should be anticipated as with any strong opioid, and treated appropriately with laxatives. Should opioid related adverse events persist, they should be investigated for an alternative cause.

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

The most serious adverse reaction, as with other opioids, is respiratory depression (see Overdose section). This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

The adverse drug reactions seen during clinical trials and from spontaneous reports are listed below. The following frequency categories form the basis for classification of the undesirable effects:

<table>
<thead>
<tr>
<th>Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 to &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1,000 to &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000 to &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>Cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>anaphylactic responses</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>syndrome of inappropriate antidiuretic hormone secretion</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>decreased appetite</td>
<td>dehydration, weight fluctuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>abnormal dreams, anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking</td>
<td>agitation, depersonalisation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Confidential  7
<table>
<thead>
<tr>
<th>Condition Type</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>somnolence, dizziness, headache</td>
<td>tremor, lethargy</td>
<td>amnesia, convulsion, hyperkinesia, hypertonia, hypoesthesia, hypotonia, involuntary muscle contractions, speech disorder, stupor, paraesthesia, dysgeusia, syncope</td>
<td>hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>visual impairment, lacrimation disorder, miosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>tinnitus, vertigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>palpitations (in the context of withdrawal syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>vasodilatation, hypotension, orthostatic hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>dyspnoea, bronchospasm,</td>
<td>rhinitis, epistaxis, hiccup, voice alteration, respiratory depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>constipation, nausea, vomiting</td>
<td>abdominal pain, diarrhoea, dry mouth, dyspepsia</td>
<td>dysphagia, flatulence, gastritis, mouth ulceration, eructation, ileus, stomatitis</td>
<td>dental caries</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>increased hepatic enzyme, biliary colic, cholestasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>pruritus</td>
<td>rash, hyperhidrosis</td>
<td>dry skin, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>urinary disorders, urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>erectile dysfunction, hypogonadism, amenorrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>asthenia, fever, fatigue</td>
<td>chills, chest pain, drug withdrawal syndrome (see sections 4.2 &amp; 4.4), gait disturbance, malaise, oedema, peripheral oedema, drug tolerance, thirst</td>
<td></td>
<td>drug withdrawal syndrome neonatal</td>
<td></td>
</tr>
</tbody>
</table>

Tolerance may occur in patients treated with oxycodone, although this has not been a significant problem in the clinical trial programme. Patients requiring marked dose escalation should have their pain control regimen carefully reviewed.

**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.
4.9. Overdose

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence, progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, pulmonary oedema and death.

Treatment of oxycodone overdose:
A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Supportive measures (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias cardiac massage or defibrillation may be indicated. If necessary, assisted ventilation as well as maintenance of water and electrolyte balance. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient’s response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

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

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone 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.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids
ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties and has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity.

Gastrointestinal system
Opioids may induce spasm of the sphincter of Oddi.
Endocrine System
See section 4.4.

Other Pharmacologic 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 semi-synthetic opioid, has immunological effects similar to morphine is unknown.

5.2. Pharmacokinetic properties

Absorption:
After administration of OxyNorm Dispersa, peak oxycodone plasma concentrations are observed after approximately 1 hour (range 0.5 – 5.0 hours). Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

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

Metabolism:
Oxycodone is metabolized 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 active drug and its metabolites are excreted in both urine and faeces. It has an elimination half-life of approximately 3 hours.

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

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

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

Patients with renal impairment:
When compared to normal subjects, patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) may have higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone, and this may be accompanied by an increase in drug effects.

5.3. Preclinical safety data
Teratogenicity
Oxycodone has shown no effect on fertility or foetal development in rats and rabbits except at doses leading to toxic effects in the dams.

Carcinogenicity
No animal studies to evaluate the carcinogenic potential of oxycodone have been conducted.

Mutagenicity
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 48 hours after exposures. 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
Sugar spheres (contains sucrose and maize starch)
Polyacrylate dispersion 30%
Hypromellose
Mannitol
Silicon dioxide
Cellulose, microcrystalline
Crospovidone
Aspartame
Spearmint flavour (contains maltodextrin and spearmint oil)
Magnesium stearate

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
3 years.

6.4. Special precautions for storage
Do not store above 25°C.

6.5. Nature and contents of container
Aluminium blister packs with a peelable aluminium backing foil.
Pack sizes: 14, 28 or 56 tablets.
Not all pack sizes may be marketed.

6.6. **Special precautions for disposal**

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. **MARKETING AUTHORISATION HOLDER**

Mundipharma Pharmaceuticals Limited
Millbank House
Arkle Road
Sandyford
Dublin 18

8. **MARKETING AUTHORISATION NUMBER**

PA 1688/006/007-009

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

Date of first authorisation: 16th July 2010
Date of latest renewal: 16th July 2015

10. **DATE OF REVISION OF TEXT**

24/05/2019