SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Oxycod 2 mg/ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml Oxycod Syrup contains oxycodone HCl 2 mg.

For the full list of excipients see section 6.1

Excipients with known effect:
Oxycod Syrup contains azorubine.
Each 1 ml Oxycod Syrup contains 0.2 mg sodium benzoate.
Oxycod Syrup contains ethanol (10%v/v, 4 gram/bottle).
Each 1 ml Oxycod Syrup contains 0.54 mg saccharin sodium and 210 mg sorbitol.
See section 4.4.

3 PHARMACEUTICAL FORM

Syrup for oral use.

Clear, pink solution.

4 CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[*see sections *4.4, 4.5]*.
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

For the relief of moderate to severe pain.

4.2 Posology and method of administration

Method *of administration:*
Oxycod Syrup is for oral use.

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

Elderly and adults over 18 years:
Oxycod Syrup 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.
Generally, the lowest effective dose for analgesia should be selected.
Increasing severity of pain will require an increased dosage of Oxycod Syrup. The correct dosage for any individual patient is that which controls the pain and is well tolerated throughout the dosing period. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this.

The usual starting dose for opioid naive patients or patients presenting with severe pain uncontrolled by weaker opioids is 5 mg, 4-6 hourly. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief.

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).

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 Oxycod Syrup required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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

Adults with mild to moderate renal impairment and mild hepatic impairment
The plasma concentration in this patient population may be increased. Therefore, dose initiation should follow a conservative approach. The starting dose for opioid naïve patients is 2.5 mg 6-hourly. See also section 4.3.

Children
Oxycod Syrup should not be used in patients under 6 years.
Doses should be titrated to appropriate effect.
0.05-0.15mg/kg/dose every 4-6 hours as needed.

Use in non-malignant pain:
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

Duration of treatment
Oxycodone should not be used for longer than necessary. In common with other strong opioids, the need for continued treatment should be assessed at regular intervals.

Discontinuation of treatment:
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

4.3 Contraindications

Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.
Oxycodone must not be used in any situation where opioids are contraindicated:

severe respiratory depression with hypoxia, paralytic ileus, acute abdomen, delayed gastric emptying, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, elevated carbon dioxide levels in the blood, moderate to severe hepatic impairment, chronic constipation.

4.4 Special warnings and precautions for use

Caution must be exercised when administering oxycodone to the debilitated elderly, opioid-dependent patients, 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 or 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).

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

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

Oxycod Syrup should be used with caution pre-operatively and 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 Oxycod Syrup for 6 hours prior to the intervention. If further treatment with oxycodone is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

Tolerance, Dependence, and Opioid Use Disorder

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

Repeated use of Oxycod Syrup 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 Oxycod Syrup 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 Oxycod Syrup and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient. 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.

Concomitant use of alcohol and Oxycod Syrup may increase the undesirable effects of Oxycod Syrup; 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.

Oxycod Syrup contains azorubin, which may cause allergic reactions.
Oxycod Syrup contains sodium benzoate (0.2 mg/ml). Sodium benzoate may increase jaundice in new-born babies (up to 4 weeks old).
Oxycod Syrup contains ethanol (10%v/v, 4 gram/bottle).
Oxycod Syrup contains saccharin sodium (0.54 mg/ml), sorbitol (210 mg/ml).
Each 1 ml of Oxycod Syrup contains less than 1 mg sodium.

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, anti-depressants, 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 Oxycod Syrup, 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
Oxycod Syrup is 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. 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.

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 know*n: 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.

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 Oxycod Syrup 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).

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Acute overdose with oxycodone can be manifested by miosis, respiratory depression and hypotension. 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.

Treatment of oxycodone overdosage: primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event 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.

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

Additional/other considerations:

- Consider activated charcoal (50 g for adults, 10-15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids
ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic 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.

5.2 Pharmacokinetic properties

Absorption
Mean peak plasma concentrations of approximately 20 ng/ml were achieved within 1.5 hours of administration, median t_{max} values from two strengths (1 mg/ml and 10 mg/ml) of liquid being less than 1 hour.

A pharmacokinetic study in healthy volunteers has demonstrated that, following administration of a single 10 mg dose, 1 mg/ml solution or 10 mg/ml syrup, provided an equivalent rate and extent of absorption of oxycodone.

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
Oxycodone has an elimination half life of approximately 3-4 hours. The active drug and its metabolites are excreted in urine.

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

5.3 Preclinical safety data

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

Sorbitol, ethanol, citric acid, saccharin sodium, tutti frutti flavor, sodium benzoate, azorubin, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25˚C. The syrup can be used within 3 months after first opening, but no later than the expiry date imprinted on the package.

6.5 Nature and contents of container

50 ml in HDPE bottles, with a child-resistance cap. A measuring cup is also supplied.

7 MARKETING AUTHORISATION

Rafa Laboratories Ltd., POB 405, Jerusalem 9100301

Drug registration number: 107-54-29027

Revised in March 2025.