OxyNorm® Capsules

Composition
Oxycodone hydrochloride Ph Eur

Oxycodone hydrochloride is a white, crystalline odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether. The chemical name is 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (CAS No: 124-90-3). The molecular formula is C_{18} $H_{21}NO_4$ HCl and molecular weight is 351.83.
The inactive ingredients in ***OxyNorm***® capsules are: microcrystalline cellulose and magnesium stearate.

The capsule shells contain sodium lauryl sulfate and gelatin. Capsule shell is derived from animal origin (bovine source).

The capsule shells also contain the following colouring materials:

	Strength	
Colouring material	**5 mg**	**10 mg**
Indigo carmine CI73015 (E132)	•	•
Iron oxide red CI77491 (E172)	•	•
Iron oxide yellow CI77492 (E172)	•	•
Sunset yellow FCF CI15985 (E110)	•	
Titanium dioxide (E171)	•	•

Indication
The management of opioid responsive, moderate to severe pain.

Administration and dosage
OxyNorm® capsules are for oral use and should be swallowed whole and not opened, chewed or crushed.

Adults and elderly over 18 years:
Prior to initiation and titration of doses, refer to the *Warnings and Precautions* section for information on special risk groups such as females and the elderly.

OxyNorm® capsules 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 ***OxyNorm***® capsules. 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.

OxyNorm® capsules will generally be used in a short term trial (4-6 weeks) to determine if the pain is opioid responsive, before transferring to a longer acting oxycodone preparation such as ***OxyContin***® tablets, in accordance with the clinical guidelines on the use of opioid analgesics in such patients.

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.

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 emphasized that this is a guide to the dose of ***OxyNorm***® capsules required. Inter-patient variability requires that each patient be 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.

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 oxycodone 6-hourly, given as ***OxyNorm***® liquid.

Paediatric population: ***OxyNorm***® capsules should not be used in patients under 18 years.

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.

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

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.

Contraindications
Hypersensitivity to oxycodone or to any of the excipients listed in *Composition.*
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.

Warnings and precautions
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 *Drug interactions and incompatibilities*).

The primary risk of opioid excess is respiratory depression.

Sleep related breathing disorders
Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing central sleep apnoea (see *Side effects*).

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 *Administration and dosage*).

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 *Drug interactions and incompatibilities*).

OxyNorm® capsules must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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

OxyNorm® capsules should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

As with all opioid preparations, ***OxyNorm***® capsules should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the doctor is assured of normal bowel function.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive ***OxyNorm***® capsules 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. See *Administration and dosage* for additional information on treatment goals and discontinuation.

Tolerance, Dependence and Opioid Use Disorder

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

Repeated use of ***OxyNorm***® capsules 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 ***OxyNorm***® capsules 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 ***OxyNorm***® capsules and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see *Administration and dosage*). 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, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, 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.

The capsules should be swallowed whole, and not chewed or crushed.

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.

Special risk groups

Renal and hepatic impairment

In renal and hepatic impairment, the administration of ***OxyNorm***® capsules 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. Therefore, initiation of dosing in patients with renal impairment (CLcr <60ml/min) or hepatic impairment should be reduced to ⅓ to ½ of the usual dose with cautious titration.

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being approximately 15% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced ⅓ to ½ of the usual doses.

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. There were no significant male/female differences detected for efficacy or adverse events in clinical trials.

Carcinogenicity/Mutagenicity

Oxycodone was not mutagenic in the Ames *Salmonella* and *E.coli* assays, but was positive in the mouse lymphoma assay. In assays of chromosomal damage, toxic effects occurred in the human lymphocyte chromosomal aberration assay *in vitro*, but not in the *in vivo* bone marrow micronucleus assay in mice. The data from these assays indicate that the genotoxic risk to humans may be considered low.

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.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of oxycodone with serotonergic drugs (See *Drug interactions and incompatibilities*). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see *Drug interactions and incompatibilities*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that.

Discontinue oxycodone if serotonin syndrome is suspected.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms

and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility. (See *Postmarketing Experience*)

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

Drugs which affect the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, anaesthetics, muscle relaxants, antihypertensives and alcohol.

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

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

MAO inhibitors are known to interact with narcotic analgesics. MAO-inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see *Warnings and precautions*). 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 ***OxyNorm***®, 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 Cmax by 11%, AUC by 13%, and t½ elim. by 14%. Also an increase in noroxycodone level was observed, (Cmax by 50%; AUC by 85%, and t½ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered.

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When

opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see *Warnings and precautions*).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Fertility, pregnancy and lactation

Pregnancy

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

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

Breastfeeding

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

Fertility

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

Effect on ability to drive and use machinery

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.

Side effects

Immediate release formulations such as ***OxyNorm***® capsules may have a higher incidence of some adverse reactions than controlled-release formulations such as ***OxyContin***® tablets. 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 following frequency categories form the basis for classification of the side 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
Psychiatric disorders	
Common	Anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking, abnormal dreams
Uncommon	Affect lability, agitation, euphoria, hallucinations, decreased libido, disorientation, mood altered, restlessness, dysphoria
Frequency not known	Aggression, drug dependence
Eye disorders	
Uncommon	Miosis, visual disturbance
Ear and labyrinth disorders	
Uncommon	Vertigo
Hepato-biliary disorders	
Uncommon	Biliary colic, increased hepatic enzymes
Frequency not known	Cholestasis, spasm of sphincter of oddi
Musculoskeletal and connective tissue disorders	
Uncommon	Muscular rigidity
Gastrointestinal	
Very common	Constipation, nausea, vomiting.
Common	Dry mouth, dyspepsia, abdominal pain, diarrhoea
Uncommon	Dysphagia, eructation, flatulence, ileus, gastritis
Frequency not known	Dental caries
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
Genitourinary	
Uncommon	Ureteric spasm, urinary retention
Cardiac disorders	
Uncommon	Supraventricular tachycardia, palpitation (as part of withdrawal syndrome)
Vascular disorders	
Uncommon	Vasodilation, facial flushing
Rare	Hypotension, orthostatic hypotension
Metabolic and Nutritional disorders	
Common	Decreased appetite

Uncommon	Dehydration
Respiratory, thoracic and mediastinal disorders	
Common	Bronchospasm, dyspnoea, cough decreased
Uncommon	Respiratory depression, hiccups
Not known	Central sleep apnoea syndrome
Dermatological disorders	
Very common	Pruritus
Common	Rash, hyperhidrosis
Uncommon	Dry skin, exfoliative dermatitis
Rare	Urticaria
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, hypogonadism
Frequency not known	Amenorrhoea
General disorders and administration site conditions	
Common	Asthenia, fatigue
Uncommon	Oedema, oedema peripheral, malaise, thirst, pyrexia, chills
Frequency not known	Drug withdrawal syndrome neonatal, opioid tolerance, opioid withdrawal syndrome

If nausea and vomiting are troublesome oxycodone may be combined with an antiemetic. Constipation must be treated with appropriate laxatives. Overdose may produce respiratory depression. Compared with other opioids oxycodone is associated with low histamine release although urticaria and pruritus may occur.

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 *Side Effects*). ‘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 ***OxyNorm®*** capsules 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 *Warning and Precautions* for monitoring and risk reduction interventions).

Postmarketing Experience
Serotonin syndrome (See *Warning and Precautions*)
Adrenal insufficiency (See *Warning and Precautions*)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Overdosage

Symptoms: Acute overdosage with oxycodone can be manifested by miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, pulmonary oedema and death may occur in more severe cases.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

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 2minute 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 empties as this can be useful in removing unabsorbed drug.

Pharmacodynamic

Oxycodone is a full opioid agonist with no antagonist properties whose principal therapeutic action is analgesia. It has affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the CNS (respiratory depression, antitussive, anxiolytic, sedative and miosis), smooth muscle (constipation, reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi and transient elevations in serum amylase) and cardiovascular system (release of histamine and/ or peripheral vasodilation, possibly causing pruritus, flushing, red eyes, sweating and/or orthostatic hypotension).

Pharmacokinetics

Absorption

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone undergoes relatively low “first pass” metabolism and has a high absolute bioavailability of up to 87% following oral administration. Peak plasma concentrations of oxycodone are reached approximately 1 hour after administration of ***OxyNorm*®** capsules.

Distribution

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

Metabolism

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

Elimination

The plasma elimination half-life is approximately 3.5 hours. The active drug and its metabolites are excreted in urine.

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.

When compared to normal subjects, patients with mild to severe renal dysfunction 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.

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.

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Presentation
OxyNorm® capsules 5 mg (orange/beige), 10 mg (white/beige), 20 mg (pink/beige), in blister packs of 28 capsules (two blister stripes of 14 capsules).
Do not store above 30°C

Product Registration Holder
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