WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, Oxycodone Sandoz should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see *section 4.4 Special Warnings and Precautions for Use*).

Hazardous and harmful use
Oxycodone Sandoz poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see *section 4.4. Special Warnings and Precautions for Use*).

Life threatening respiratory depression
Serious, life-threatening or fatal respiratory depression may occur with the use of Oxycodone Sandoz. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see *section 4.4 Special Warnings and Precautions for Use*).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol
Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking Oxycodone Sandoz.

1 PRODUCT NAME

OXYCODONE SANDOZ® modified release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxycodone Sandoz 5mg tablets – each tablet contains Oxycodone hydrochloride 5mg
Oxycodone Sandoz 10mg tablets – each tablet contains Oxycodone hydrochloride 10mg
Oxycodone Sandoz 20mg tablets – each tablet contains Oxycodone hydrochloride 20mg
Oxycodone Sandoz 40mg tablets – each tablet contains Oxycodone hydrochloride 40mg
Oxycodone Sandoz 80mg tablets – each tablet contains Oxycodone hydrochloride 80mg

Excipient with known effect: lactose monohydrate

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release tablets.

Oxycodone Sandoz 5mg – round, blue, biconvex, modified release tablets

Oxycodone Sandoz 10mg – round, white, biconvex, modified release tablets

Oxycodone Sandoz 20mg – round, pink, biconvex, modified release tablets

Oxycodone Sandoz 40mg – round, yellow, biconvex, modified release tablets

Oxycodone Sandoz 80mg – round, green, biconvex, modified release tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

4.2 Dose and method of administration

Oxycodone Sandoz tablets 80 mg should only be used in opioid-tolerant patients. In patients not previously exposed to opioids (opioid naïve), these tablet strengths may cause fatal respiratory depression.

Oxycodone Sandoz tablets are to be swallowed whole, and are not to be broken, chewed or crushed. Taking broken, chewed or crushed Oxycodone Sandoz tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

Alcoholic beverages should be avoided while the patient is being treated with Oxycodone Sandoz tablets.

Treatment goals and discontinuation

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

Duration of treatment

Oxycodone should not be used for longer than necessary.

Adults and children over 12 years:

Prior to initiation and titration of doses, refer to section 4.4 for information on ***special risk groups*** such as females and the elderly. Oxycodone Sandoz tablets should be taken at 12-hourly intervals. Appropriate pain management principles of careful assessment and ongoing monitoring should be followed at regular intervals, including reassessing the need for

continued opioid therapy. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

The usual starting dose for opioid-naive patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg 12-hourly. The dose should then be carefully titrated, as frequently as once a day if necessary, with patient monitoring, assessing whether the pain is opioid responsive and providing the patient significant pain relief.

Increasing severity of pain will require an increased dosage of Oxycodone Sandoz tablets using the 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated, for a full 12 hours. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the patient should be reassessed and, only if appropriate that the dosage of Oxycodone Sandoz tablets should be increased.

Conversion from oral morphine:

Patients receiving oral morphine before Oxycodone Sandoz tablet 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 only a guide to the dose of Oxycodone Sandoz tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Patients transferring from other opioid formulations:

Patients receiving other oral oxycodone formulations may be transferred to Oxycodone Sandoz tablets at the same total daily dosage, equally divided into two 12-hourly Oxycodone Sandoz tablet doses.

For patients who are receiving an alternative opioid, the "oral oxycodone equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, the following equivalence table can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. The total daily oral oxycodone dosage should then be equally divided into two 12-hourly Oxycodone Sandoz tablet doses.

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*		
(mg/Day Prior Opioid x Factor = mg/Day Oral Oxycodone)		
	Oral Prior Opioid	Parenteral Opioid
Oxycodone	1	-
Codeine	0.15	-
Fentanyl TTS	See below **	See below**
Hydromorphone	4	20
Pethidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* To be used for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

** Conversion from transdermal fentanyl to Oxycodone Sandoz tablets: 18 hours following the removal of the transdermal fentanyl patch, Oxycodone Sandoz tablet treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-hourly of Oxycodone Sandoz tablets, should be initially substituted for each 25µg/hr fentanyl transdermal patch. The patient should be followed closely.

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.

Children under 12 years:

Not recommended.

Patients with renal or hepatic impairment:

The dose titration should follow a conservative approach in these patients. The recommended adult starting dose in patients with renal impairment (CrCl<60mL/min) or hepatic impairment should be reduced by $^1/_3$ to $^1/_2$, and each patient should be titrated to adequate pain control according to their clinical situation (see Section 4.4 Special warnings and precautions for use).

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 opioids or to any of the constituents of Oxycodone Sandoz tablets,
- acute respiratory disease,
- severe respiratory disease,
- respiratory depression,
- *cor pulmonale*,
- cardiac arrhythmias,
- acute asthma or other obstructive airways disease,
- suspected mechanical gastrointestinal obstruction (e.g. bowel obstruction, strictures) or any diseases/ conditions that affect bowel transit (paralytic ileus or ileus of any type),
- suspected surgical abdomen,
- severe renal impairment (creatinine clearance < 10 mL/min),
- severe hepatic impairment (refer to section 4.4),
- delayed gastric emptying,
- acute alcoholism,
- brain tumour,
- increased cerebrospinal or intracranial pressure,
- head injury (due to risk of raised intracranial pressure),
- severe CNS depression,

- convulsive disorders,
- delirium tremens,
- hypercarbia,
- concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use,
- Not recommended for pre-operative use or for the first 24 hours post-operatively,
- pregnancy.

4.4 Special warnings and precautions for use

Oxycodone has to be administered with caution in patients with:

- Hypotension
- Severely impaired renal function,
- Myxedema,
- Prostate hypertrophy
- Hypovolaemia

Hazardous and harmful use

Oxycodone Sandoz contains the opioid oxycodone and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Oxycodone Sandoz at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed Oxycodone Sandoz.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal)*. Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Repeated use of oxycodone can 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 oxycodone may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or 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 oxycodone and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2 Dose and Method of Administration). 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). This includes the 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.

Patients should be advised not to share Oxycodone Sandoz with anyone else.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Oxycodone Sandoz with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe Oxycodone Sandoz concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5 Interactions with other medicines and other forms of interaction).

Advise both patients and caregivers about the risks of respiratory depression and sedation when Oxycodone Sandoz is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5 Interactions with other medicines and other forms of interaction).

Tolerance, physical dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea,

yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing Oxycodone Sandoz in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2 Dose and method of administration).

One doctor only should be responsible for the prescribing and monitoring of the patient's opioid use.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see *section 4.2 Dose and Method of Administration*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Accidental ingestion/exposure

Accidental ingestion or exposure of Oxycodone Sandoz, especially by children, can result in a fatal overdose of oxycodone. Patients and their caregivers should be given information on safe storage and disposal of unused Oxycodone Sandoz (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for handling, reconstitution and disposal*.

Respiratory depression and sedation

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Oxycodone Sandoz but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with renal and hepatic impairment and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 Dose and

method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2 Dose and method of administration) together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response. The major risk of opioid excess is respiratory depression, including subclinical 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. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8 Undesirable effects). In patients who present with CSA, consider decreasing the total opioid dosage.

Effects on hypothalamic-pituitary-adrenal or gonadal axes

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. As with all opioids, a reduction in dosage may be advisable in hypothyroidism.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Pre and post-operative use

As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive Oxycodone Sandoz tablets for 24 hours before surgery. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with Oxycodone Sandoz tablets is then indicated the dosage should be adjusted to the new post-operative requirement. As with all opioid preparations, Oxycodone Sandoz tablets 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. Should paralytic ileus be suspected or occur during use, Oxycodone Sandoz tablets should be discontinued immediately.

Psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse

There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. Oxycodone Sandoz tablets should be used with particular care in patients with a history of substance misuse disorder (including alcohol misuse) or mental health

disorder. Parenteral abuse of dosage forms not approved for parenteral administration can be expected to result in serious adverse events, which may be fatal.

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

The use of Oxycodone Sandoz tablets for the treatment of chronic pain which is not due to malignancy should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed
- the pain is having a significant impact on the patient's quality of life

- there is no psychological contraindication, drug-seeking behaviour or history of drug misuse.

Appropriate patient selection is the key to successful treatment of moderate to severe pain with opioid analgesics.

An initial comprehensive assessment should be conducted using a biopsychosocial approach to identify a cause for the pain and the appropriateness of opioid therapy — and to identify psychosocial factors that may exacerbate pain or magnify overall distress (e.g. depression, anxiety, post-traumatic stress disorder, borderline personality disorder, marked family stressors, history of sexual abuse). In the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Factors that may put the patient at increased risk of opioid abuse/addiction include a personal/family history of substance, prescription medication and alcohol abuse, and major psychosocial issues (e.g. psychological/psychiatric disorder). The use of opioids to treat predominant emotional distress should be avoided.

Generally, opioid analgesics are not initiated prior to a full initial clinical assessment and before consideration of other treatment options such as physiotherapy/exercise/rehabilitation approaches, psychosocial interventions such as CBT (cognitive-behavioural therapy) self-management approaches, involvement of a psychologist or psychiatrist to address psychological co-morbidities which may be impacting on pain coping and trials of other non-opioid pharmacotherapeutic or interventional strategies.

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.

Adrenal insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with Oxycodone Sandoz should be considered.

Neonatal withdrawal syndrome

Chronic use of oxycodone by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section 4.6 Fertility, pregnancy and lactation).

Gastrointestinal toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

Formulation

Oxycodone Sandoz tablets are intended for oral use only. The modified release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed modified release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. Use caution when prescribing oxycodone tablets for patients who have any underlying GI disorders that may predispose them to intestinal obstruction. Patients with underlying GI disorders such as oesophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk. Oxycodone tablets should not be taken by patients with difficulty in swallowing or who have been diagnosed with narrowing of the oesophagus. If patients experience swallowing difficulties (e.g. choking, gagging, discomfort, regurgitation, tablets stuck in the throat) after taking oxycodone tablets, they should be advised to seek immediate medical attention. Parenteral venous injection of the tablet constituents can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

Special Risk Groups

Use in renal and hepatic impairment

In renal and hepatic impairment, the administration of Oxycodone Sandoz tablets 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 (CrCl < 60 mL/min) or hepatic impairment should be reduced to $^1/_3$ to $^1/_2$ of the usual dose with cautious titration.

Use in elderly

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

Use in elderly, debilitated patients

As with other opioid initiation and titration, doses in elderly patients who are debilitated should be reduced to $^1/_3$ to $^1/_2$ of the usual doses.

Paediatric use

Oxycodone is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

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.

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic agents

Concurrent use of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson medications) may result in increased anticholinergic adverse effects, including an increased risk of severe constipation and/or urinary retention.

Antihypertensive agents

Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.

CNS depressants

The concomitant use of oxycodone with CNS depressants increase the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Caution is recommended and the dosage of one or both agents should be reduced. The dose and duration of concomitant use should be limited (see section 4.4 Special warnings and precautions for use). CNS depressants include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (incl. benzodiazepines), tranquilizers, muscle relaxants, drugs with antihistamine-sedating actions such as antipsychotics, antidepressants, phenothiazines and alcohol.

Intake of alcoholic beverages while being treated with Oxycodone Sandoz tablets should be avoided because this may lead to more frequent undesirable effects such as somnolence and respiratory depression. Oxycodone hydrochloride containing products should be avoided in patients with a history of or present alcohol, drug or medicines abuse.

Coumarin derivatives

Although there is little substantiating evidence, opiate agonists have been reported to potentiate the anticoagulant activity of coumarin derivatives.

A clinically relevant decrease or increase of INR (International Normalised Ratio, Quick's test) has been observed in individual cases in simultaneous use of oxycodone and coumarin anticoagulants.

CYP2D6 and CYP3A4 inhibitors and inducers

Oxycodone is metabolised in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly. 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 does not alter the pharmacodynamic effects of oxycodone. CYP3A4 inhibitors such as macrolide antibiotics (e.g. clarithromycin), azole antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir) and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Oxycodone metabolism may be blocked by a variety of medicines (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with Oxycodone Sandoz tablets.

CYP3A4 inducers, such as rifampin, carbamazepine, phenytoin and St John's wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations.

Oxycodone did not inhibit the activity of P450 isozymes 2D6, 3A4, 1A2, 2A6, 2C19 or 2E1 in human liver microsomes *in vitro.* Nonclinical data *in vitro* and *in vivo* indicate that oxycodone can act as a P-glycoprotein substrate and can induce overexpression of P-glycoprotein in rats.

Metoclopramide

Concurrent use with oxycodone may antagonise the effects of metoclopramide on gastrointestinal motility.

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of opioid medicines which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAOIs and pethidine. Oxycodone should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. As it is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and oxycodone, caution is advised with this medicine combination.

Neuromuscular blocking agents

Oxycodone may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Opioid agonist analgesics (including morphine, pethidine)

Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

Opioid agonist-antagonist analgesics (including pentazocine, butorphanol, buprenorphine)

Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms.

Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI)

Concurrent 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, diarrhea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

Australian Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Oxycodone passes the placenta.

Oxycodone used during pregnancy or labour may cause withdrawal symptoms and/or respiratory depression in the newborn infant. Oral administration of oxycodone during the period of organogenesis did not elicit teratogenicity or embryofoetal toxicity in rats or rabbits at doses up to 8 mg/kg/day in rats (equivalent to 17 mg/day in women, based on estimated plasma AUC values) or 125 mg/kg/day in rabbits.

Oral administration of oxycodone to rats from early gestation to weaning did not affect postnatal development parameters at doses up to 6 mg/kg/day (equivalent to 9 mg/day in women, based on estimated AUC values). In a study designed specifically to investigate the effect of pre-natal oxycodone on the hypothalamic-pituitary-adrenal axis in adolescent rats, intravenous administration of oxycodone 0.8 mg/kg/day (equivalent to 11 mg/day in pregnant women, based on estimated AUC values) had no effect on the corticosterone response, but delayed and enhanced the peak ACTH response to corticotrophin releasing hormone in males, but not females. The clinical significance of this observation is unknown.

There are no adequate and well-controlled studies with oxycodone in pregnant women. Because animal reproduction studies are not always predictive of human responses, oxycodone should not be used during pregnancy unless clearly needed. Prolonged use of oxycodone during pregnancy can result in neonatal opioid withdrawal syndrome. Oxycodone is not recommended for use in women during or immediately prior to labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

Use in lactation

Oxycodone accumulates in human milk, with a median maternal milk:plasma ratio of 3:1 recorded in one study. Oxycodone (7.5 ng/mL) was detected in the plasma of one of forty-one infants 72 hours after Caesarean section. Opioids may cause respiratory depression in the newborn and withdrawal symptoms can occur in breast feeding infants when maternal administration of an opioid analgesic is stopped. Oxycodone Sandoz tablets should not be used in breast feeding mothers unless the benefits outweigh the risks. Breastfed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

Effects on fertility

In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at oral oxycodone doses of 8 mg/kg/day, with estimated exposure (plasma AUC) equivalent to 8 mg/day in men and 17 mg/day in women.

Despite these fertility studies in animals, prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes, and irregular menses in women.

4.7 Effects on ability to drive and use machines

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If their ability is impaired, patients should not drive or operate machinery. This is particularly likely at the initiation of treatment with oxycodone, after dose increase or product rotation and if oxycodone combined with other CNS depressant agents. Patients stabilised on a specific dose will not necessarily be restricted. Therefore, the physician should decide whether the patient is allowed to drive or use machines.

4.8 Undesirable effects

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.

Tabulated summary of adverse reactions

	Very Common (≥ 1/10)	Common (1/100 to <1/10)	Uncommon (1/1,000 to <1/100)	Not known
Immune system disorders			allergic reaction, anaphylactic reaction, anaphylactoid reaction, hypersensitivity	
Metabolic and nutritional disorders		decreased appetite	increased appetite, dehydration, hyponatraemia	
Psychiatric disorders		abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression	affect lability, agitation, disorientation, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness	aggression, drug dependence* (see section 4.4)
Nervous system disorders	dizziness, headache, somnolence	faintness, sedation, twitching, tremor, lethargy	amnesia, drowsiness, abnormal gait, convulsion, dysgeusia (taste perversion), hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, muscle contractions involuntary, paraesthesia, seizures, speech disorder, stupor, syncope	hyperalgesia
Eye disorders			miosis, visual impairment	
Ear and labyrinth disorders			tinnitus, vertigo	
Endocrine disorders				adrenal insufficiency, androgen deficiency
Cardiac disorders			bradycardia, chest pain, palpitations (as part of withdrawal syndrome), ST depression, supraventricular tachycardia	
Vascular disorders		orthostatic hypotension	hypotension, migraine, vasodilatation	
Respiratory, thoracic and mediastinal disorders		bronchospasm, dyspnoea, pharyngitis, voice alteration	respiratory depression, choking	central sleep apnoea syndrome
Gastrointestinal disorders	nausea, vomiting, constipation	abdominal pain, diarrhoea, dry mouth, dyspepsia, gastritis, hiccup	colic, dental caries, dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, stomatitis, regurgitation, retching	pancreatitis
Hepatobiliary disorders			biliary spasm, cholestasis, hepatic enzyme increased	Sphincter of Oddi dysfunction
Injury, poisoning and procedural complications			medication struck in throat	
Skin and subcutaneous tissue disorders	pruritus	hyperhidrosis, rash	dry skin, exfoliative dermatitis, urticaria and other skin rashes	
Renal and urinary disorders			ureteric spasm, urinary abnormalities, urinary retention, urinary tract infection	
Reproductive system and breast disorders			amenorrhoea, erectile dysfunction, hypogonadism	

	Very Common (≥ 1/10)	Common (1/100 to <1/10)	Uncommon (1/1,000 to <1/100)	Not known
General disorders and administration site conditions		asthenia, fatigue, chills, fever	accidental injury, facial flushing, lymphadenopathy, malaise, muscular rigidity, neck pain, oedema, peripheral oedema, pain, thirst	drug withdrawal syndrome neonatal, opioid tolerance*, opioid withdrawal syndrome*

* The frequency of drug dependence, opioid tolerance and 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". 'Not known' should not be interpreted as an indication of the rarity of the occurrence of drug dependence, 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.

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.

Drug dependence

The frequency in the above table 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 the occurrence of drug dependence, but a reflection of the limitations in the available evidence that do not support a precise estimate of frequency.

Repeated use of oxycodone 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 Special Warnings and Precautions for Use).

As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), addiction, abuse, and misuse, as well as opioid use disorder and problematic opioid use. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oxycodone. Addiction can occur at recommended doses, and if the drug is misused or abused. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The frequency of drug dependence also increases with longer term use or higher doses of oxycodone (See section 4.4 Special Warnings and Precautions for Use).

Opioid Tolerance and Opioid Withdrawal Syndrome

The frequency of in the above table regarding opioid tolerance and opioid withdrawal syndrome reflects the high variability of risk depending upon: definition of tolerance and withdrawal syndrome; dose and duration of treatment; and assessment and monitoring methods (specific to withdrawal syndrome). '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. As an opioid, oxycodone exposes users to the risks of dependence (both physical and psychological), tolerance and withdrawal syndrome (see section 4.4 Special Warnings and Precautions for Use).

Post-marketing

There have been rare post-marketing cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet.

There have been uncommon post-marketing reports of difficulty swallowing oxycodone 10 mg to 80 mg tablets, potentially due to the swelling and hydrogelling property of the tablets: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Reporting of suspected adverse reactions

Reporting suspected adverse reaction after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms

Acute overdosage with oxycodone can be manifested by respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, hypotonia, skeletal muscle flaccidity, cold and/or clammy skin, miosis (dilated if hypoxia is severe), and sometimes bradycardia, hypoglycemia, hypotension, and death. Severe overdose may result in apnoea, pulmonary oedema, circulatory collapse and death. Toxic leukoencephalopathy has been observed with oxycodone overdose. The features of overdose may be delayed with a sustained release product such as Oxycodone Sandoz tablets.

Treatment of Oxycodone Overdosage

Primary attention should be given to immediate supportive therapy with the establishment of adequate respiratory exchange through the provision of a patient airway and institution of assisted or controlled ventilation. Adequate body temperature and fluid balance should be maintained. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. Administration of activated charcoal should be restricted to patients who are fully conscious with an intact gag reflex or protected airway. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Whole bowel irrigation (e.g. 1 or 2 litres of polyethylene glycol solution orally per hour until rectal effluent is clear) may be useful for gut decontamination. Whole bowel irrigation is contraindicated in patients with bowel obstruction, perforation, ileus, haemodynamic instability or compromised, unprotected airways and should be used cautiously in debilitated patients and where the condition may be further compromised. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the effectiveness of the charcoal (there may be competition for the charcoal binding site between the polyethylene glycol and the ingested drugs) but the clinical relevance is uncertain. Prolonged periods of observation (days) may be required for patients who have overdosed with long-acting oxycodone preparations.

If there are signs of clinically significant respiratory or cardiovascular depression, the use of an opioid antagonist should be considered. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression due to overdosage or as a result of unusual sensitivity to opioid. The usual intravenous adult dose of naloxone is 0.4 mg or higher (please refer to naloxone data sheet for further information). The onset of naloxone effect may be delayed by 30 minutes or more. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of oxycodone, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed, or an antagonist infusion established, to maintain adequate respiration.

In an individual physically dependent on, or tolerant to, opioids, the administration of the usual dose of opioid antagonist can precipitate an acute withdrawal syndrome. This may lead to agitation, hypertension, tachycardia and risk of vomiting with possible aspiration. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Toxicity

Oxycodone toxicity may result from overdosage but because of the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Crushing and taking the contents of a modified release dosage form leads to the release of oxycodone in an immediate fashion; this might result in a fatal overdose. The toxic effects and signs of overdosage may be less pronounced than expected, when pain and/or tolerance are manifest.

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for risk assessment and advice on management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids ATC code: N02A A05

Non-proprietary name: Oxycodone hydrochloride

Chemical name: 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

CAS NO.: 124-90-3

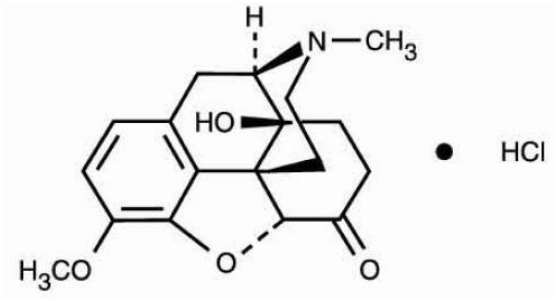
Molecular formula (anhydrous form): $C_{18}H_{21}NO_4HCI$

Molecular weight (anhydrous form): 351.83

Molecular formula (monohydrate form): $C_{18}H_{21}NO_4HCI.H_2O$

Molecular weight (monohydrate form): 369.84

Structural formula:



Oxycodone hydrochloride is a white, crystalline, odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether.

Actions

Oxycodone is a full opioid agonist with no antagonist properties whose principal therapeutic action is analgesia. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the central nervous system (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 vasodilatation, possibly causing pruritus, flushing, red eyes, sweating and/or orthostatic hypotension).

Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

CLINICAL TRIALS

A recent study assessed the effects of a standard high-fat meal on the pharmacokinetics of oxycodone 160 mg (not registered in New Zealand) in 30 healthy males and found that the C_{max} was increased by a mean of 25% (range 8 to 52%), and the overall bioavailability (AUC_{inf}) by an average of 14%. As the Mean Residence Time (MRT) was unchanged in the presence of food (9.4 hours fasting, 9.3 hours fed), the change in C_{max} may have been partly due to an increase in the extent of absorption, rather than solely due to an increased rate of absorption. There was no evidence of dose dumping, and the 90% Cls around the AUC ratios were within the range 80 to 125%.

A second recent study compared the effects of a high-fat meal on two 5 mg oxycodone tablets taken by 24 healthy males. The C_{max} was increased by a mean of 29% and the AUC_{inf} by an average of 14.5%. Again, there was no evidence of dose dumping.

5.2 Pharmacokinetic properties

Absorption

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration.

The absorption of oxycodone from Oxycodone Sandoz tablets could be calculated biphasic with an initially relatively rapid half-life of 0.6 hours accounting for a minority of the active substance, and a slower half-life of 6.9 hours accounting for the majority of the active substance.

Oxycodone Sandoz tablets are expected to provide onset of analgesia within one hour in most patients with a 12 hour duration of action. Steady state is achieved in about one day.

Following single dose oral administration of Oxycodone Sandoz tablets to healthy subjects under fasting conditions, mean peak plasma concentrations of oxycodone were achieved within 2-4 hours.

Release of oxycodone from Oxycodone Sandoz tablets is independent of pH under physiological conditions.

Oxycodone Sandoz tablets 5 mg, 10 mg, 20 mg, 40 mg and 80 mg are dose-proportional in terms of both rate and extent of absorption.

Earlier bioequivalence studies indicated that ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption however, two later studies on the lowest (5 mg) and highest (160 mg not registered in New Zealand) oxycodone strengths suggested that a high-fat meal increased the AUC by up to 20% and the C_{max} by up to 29%.

Distribution

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

Elimination

The plasma elimination half-life is approximately 4.5 hours. The active drug and its metabolites are excreted in both urine and feces. The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. 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.

5.3 Preclinical safety data

Reproductive and Developmental Toxicology

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. 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 fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal 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/day compared to the control group. Body weights were lower in the F1 generation from maternal

rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioral and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

Carcinogenicity

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

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 g/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 48 hours after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients core:

- behenoyl polyoxylglycerides,
- colloidal anhydrous silica,
- copovidone,
- hydrogenated castor oil,
- lactose monohydrate
- magnesium stearate.
- maize starch,
- medium chain triglycerides,

Excipients coating:

- hypromellose,
- microcrystalline cellulose,
- stearic acid,
- titanium dioxide,
- indigo carmine aluminium lake (5mg tablets only),

- iron oxide red (20mg tablets only),
- iron oxide yellow (40mg tablets only),
- iron oxide black (80mg tablets only) and
- 815063 Spectracol Green Lake (80mg tablets only).

6.2 Incompatibilities

None applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister packs or bottles of 20, 28 or 60 tablets.

Not all pack type/sizes of all strengths are available in NZ.

6.6 Special precautions for handling, reconstitution and disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Controlled Drug B3.

8 SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9 DATE OF FIRST APPROVAL

30 Jun 2016

10 DATE OF REVISION OF THE TEXT

6 Mar 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Revised dosing recommendations for adults and children over 12 years Minor editorial change
4.3	Added severe renal impairment and pregnancy to contraindications
4.4	Inclusion of "patients with renal and hepatic impairment" under "Respiratory despression" Additional warning subsections added for "Adrenal insufficiency", "Neonatal withdrawal syndrome" and "Gastrointestinal toxicity" Inclusion of androgen deficiency statement under "Effects on hypothalamic-pituitary-adrenal or gonadal axes" Minor editorial change
4.8	Additional subsection "Endocrine disorders" with side effects of Not Known frequency Additional side effect under "Gastrointestinal disorders" subsection with Not Known frequency
4.9	Added risk assessment wording