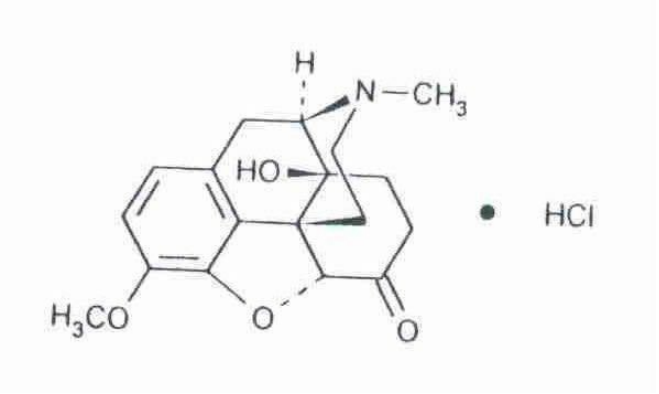
PRODUCT INFORMATION

OxyContin® Controlled Release Tablets (10 mg, 20 mg)

CAUTION: This preparation maybe habit-forming on prolonged use

NAME OF THE MEDICINE
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): $C_{18}H_{21}NO_4.HCl$ Molecular weight (anhydrous form): 351.83
Molecular formula (monohydrate form): $C_{18}H_{21}NO_4.HCl.H_20$ Molecular weight (monohydrate form): 369.84
Structural formula (anhydrous form):



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

OxyContin tablets are modified release tablets designed to provide delivery of oxycodone over 12 hours.

OxyContin 10 mg and 20 mg tablets have been reformulated, and comprise a matrix formulation with a hydrogelling property (i.e. particles or whole tablets become highly viscous (gel-like) in water), intended to be crush-deterrent and to reduce the rapid release of oxycodone upon accidental or intentional misuse. The tablets have been heat-treated to increase the mechanical strength of the tablet.

The physical properties of the reformulated *OxyContin* tablets were examined following an extensive battery of physical manipulations. Beyond demonstrating that the reformulated *OxyContin* tablets are harder to crush than another controlled release oxycodone formulation, testing over the range of the reformulated *OxyContin* tablets fragment sizes showed that some of the controlled release properties were still retained. Hydrogelling properties continued to be demonstrated.

The inactive ingredients in the reformulated *OxyContin* 10mg and 20 mg tablets are: polyethylene oxide, butylated hydroxytoluene (BHT) and magnesium stearate. The tablets' film coating also contain: Opadry Y-5-18024-A White (US version) (ARPING No. 3548) (10mg), Opadry YS- 1- 14518-A Pink (ARPING No. 3547) (20mg).

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

DOSAGE AND ADMINISTRATION
***OxyContin* tablets 80 mg should only be used in opioid-tolerant patients. These tablet strengths may cause fatal respiratory depression in patients not previously exposed to opioids (opioid naïve).**

***OxyContin* tablets are to be swallowed whole, and are not to be cut, broken, chewed, crushed or dissolved. The tablets have been hardened to reduce the risk of being accidently or intentionally broken, chewed or crushed. Taking cut, broken, chewed, crushed or dissolved *OxyContin* tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.**

To avoid difficulty swallowing, *OxyContin* tablets should not be pre-soaked, licked or otherwise wetted prior to placing in the mouth and should be taken one tablet at a time with enough water to ensure complete swallowing immediately after placing it in the mouth.

There are no data on rectal administration of *OxyContin* tablets, therefore rectal administration of *OxyContin* tablets is not recommended.

Do not administer *OxyContin* tablets via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes.

It is recommended that patients take the medication in a consistent manner in relation to the timing of meals.

Alcoholic beverages should be avoided by patients while being treated with *OxyContin* tablets.

<u>Treatment goals and discontinuation</u>
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 *PRECAUTIONS*).

<u>Adults, elderly and children over 12 years</u>
Prior to initiation and titration of doses, refer to the **PRECAUTIONS** section for information on special risk groups such as females and the elderly. *OxyContin* 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-naïve patients or patients presenting with severe pain uncontrolled by weaker opioids (especially if they are receiving concurrent sedatives, muscle relaxants or other CNS medicines) is 10 mg 12-hourly.

The dose should then be carefully titrated with longitudinal patient monitoring, assessing whether the pain is opioid responsive and providing the patient significant pain relief.

Increasing severity of pain may require an increased dosage of *OxyContin* tablets to achieve a stable dose that provides acceptable 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.

Patients who experience breakthrough pain may require dosage adjustment or rescue medication. The need for rescue medication more than twice a day indicates that the patient should be reassessed and, only if appropriate, the dosage of *OxyContin* tablets should be increased. There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.

Patients receiving oral morphine before *OxyContin* 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 is emphasised that this is a guide to the dose of *OxyContin* tablets required only. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

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

Children under 12 years
OxyContin tablets are not recommended for children under 12 years of age.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by ⅓ to ½, and each patient should be titrated to adequate pain control according to their clinical situation (see **PRECAUTIONS**, Special Risk Groups).

Patients transferring from other opioid formulations
Patients receiving other oral oxycodone formulations may be transferred to *OxyContin* tablets at the same total daily dosage, equally divided into two 12-hourly *OxyContin* 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 *OxyContin* 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 *OxyContin* tablets: 18 hours following the removal of the transdermal fentanyl patch, *OxyContin* tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg 12-hourly of *OxyContin* tablets, should be initially substituted for each 25 μg/hr fentanyl transdermal patch. The patient should be followed closely.

CONTRAINDICATIONS

Hypersensitivity to opioids or to any of the constituents of *OxyContin* 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 (e.g. ileus of any type), suspected surgical abdomen, severe renal impairment (creatinine clearance < 10 mL/min), severe hepatic impairment (refer to Special Risk Groups), 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.

PRECAUTIONS

Hazardous and Harmful use

OxyContin tablets contains the opioid oxycodone hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed *OxyContin* tablets 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 *OxyContin* tablets.

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. 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 *DOSAGE AND 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 *OxyContin* tablets with anyone else.

Respiratory depression
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 *OxyContin* tablets 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 *DOSAGE AND ADMINISTRATION*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see *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 *DOSAGE AND 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.

Sleep related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, considering decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing sleep apnoea (see *ADVERSE EFFECTS*).

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 *OxyContin* tablets 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 *OxyContin* tablets 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. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking *OxyContin* tablets.

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 *PRECAUTIONS*: 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 *PRECAUTIONS*: Ceasing Opioids).

Tolerance, 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 *OxyContin* tablets in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *PRECAUTIONS*: Ceasing Opioids).

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

Accidental ingestion/exposure
Accidental ingestion or exposure of *OxyContin* tablets, especially by children, can result in a fatal overdose of *OxyContin* tablets. Patients and their caregivers should be given information on safe storage and disposal of unused OxyContin.

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 *PRECAUTIONS*: 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.

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 *PRECAUTIONS*: 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. 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.

<u>Drug abuse studies</u>
Intranasal abuse
In a human abuse liability study, milled *OxyContin* 30 mg tablets produced subjective responses on each of the four established primary measures that were greater than placebo but significantly less than the responses for another, conventional finely crushed controlled release oxycodone tablets formulation 30 mg, or a fine powder of oxycodone 30 mg when administered intranasally in healthy recreational opioid users with a history of intranasal drug abuse/misuse (n=27). The primary measures were: 'Drug-liking 'at this moment''; 'Overall drug liking'; 'Subjective Drug Value'; 'Addiction Research Centre Inventory (ARCI) Morphine Benzedrine Group (MBG)' scales.

Objective measures of pupil diameter and other subjective measures were consistent with a lower opioid effect. Measurements of intranasal irritation showed increased irritation, particularly

related to nasal stuffiness, with OxyContin tablets compared with another conventional controlled release oxycodone tablets formulation or oxycodone powder.

In a tolerability and safety study with healthy subjects under fasting conditions, milled *OxyContin* tablets were shown to cause increased nasal discomfort, particularly related to increased nasal stuffiness, and a decrease in runny nose scores when compared with another finely milled controlled release oxycodone tablets formulation, when administered intranasally. Although total AUC was similar for all treatments, C_{max} was 67% for coarsely and 77.6% for finely milled *OxyContin* tablets (Ratio of metric means expressed as a percent, transformed back to the linear scale) compared with the other finely milled conventional controlled release oxycodone tablets formulation and T_{max} was later with *OxyContin* tablets.

An additional study was conducted to assess the administration site safety and tolerability of intranasally administered milled *OxyContin* tablets placebo vs another crushed conventional controlled release oxycodone tablets formulation placebo. Endoscopy photographs showed residual particles in the nasal cavity at 30 minutes following administration of *OxyContin* tablets placebo.

Accidental or Intentional Oral Misuse
A study in healthy subjects was conducted to characterize the impact of chewing intact and tampered tablets and subsequent swallowing, on the pharmacokinetics of *OxyContin* tablets under fasting conditions. The manufacturing process for *OxyContin* tablets imparts increased hardness to the tablets. Subjects were required to complete a chewing qualification assessment prior to receiving their initial study doses.

The results showed that under both normal and vigorous chewing conditions, *OxyContin* tablets retained some of their controlled release characteristics. Peak plasma levels of oxycodone (C_{max}) for *OxyContin* tablets were 13.5% lower when swallowed after vigorous chewing and 23.6% lower when swallowed after normal chewing (Ratio of metric means expressed as a percent, transformed back to the linear scale) when compared with another chewed conventional formulation of controlled release oxycodone tablets. The time to reach peak plasma levels (T_{max}) was also delayed for *OxyContin* tablets compared with the other conventional controlled release oxycodone tablet formulation, under both vigorous (1.5 vs 1.0 hours respectively) and normal (2.38 vs 1.13 hours respectively) chewing conditions.

<u>Formulation</u>
OxyContin 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. 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.

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.

Use in hepatic impairment
In hepatic impairment, the administration of *OxyContin* 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 hepatic function. Therefore, initiation of dosing in patients with hepatic impairment should be reduced to ⅓ to ½ of the usual dose with cautious titration.

Use in renal impairment
In renal impairment, the administration of *OxyContin* 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 function. Therefore, initiation of dosing in patients with renal impairment (CrCl< 60 mL/min) should be reduced to ⅓ to ½ of the usual dose with cautious titration.

Use in the 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.

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

Paediatric use
OxyContin tablets are not recommended for use in children under 12 years of age (See *DOSAGE AND ADMINISTRATION*).

Effects on laboratory tests
No data available.

Special Risk Patients
As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, sleep apnoea, constipation, myxoedema. As with all opioid preparations, patients who are to undergo cordotomy or other pain-relieving surgical procedures should not receive *OxyContin* 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 OxyContin tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

As with all opioid preparations, OxyContin 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, OxyContin tablets should be discontinued immediately.

Use caution when prescribing OxyContin 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.

OxyContin 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 OxyContin tablets, they should be advised to seek immediate medical attention.

Endocrine effects
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.

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*)

INTERACTIONS WITH OTHER MEDICINES

Anticholinergic agents

Concurrent use with oxycodone with anticholingerics 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

Concurrent use of oxycodone with CNS depressants (include, but are not limited to: sedatives(including benzodiazepines antipsychotics, antidepressants, anxiolytics, centrally-active anti-emetics, cannabis, hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids, gabapentinoids such as pregabalin and neuroleptic drugs, etc.)increases the risk of profound sedation,respiratory depression, hypotension, death or coma because of additive CNS depressant effects (see *PRECAUTIONS*: *Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol*).

Intake of alcoholic beverages while being treated with *OxyContin* 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.

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 drugs (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with *OxyContin* 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.* Non-clinical 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 drugs 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 drug 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.

FERTILITY, PREGNANCY AND LACTATION
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.

Use in pregnancy

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 embryo fetal 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. 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 breastfeeding infants when maternal administration of an opioid analgesic is stopped. *OxyContin* tablets should not be used in breastfeeding mothers unless the benefits outweigh the risks. Breastfed infants should be monitored for respiratory depression, sedation, poor attachment and gastrointestinal signs.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Oxycodone may cause drowsiness and modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. If affected do not drive or operate machinery.

ADVERSE 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.

Cardiac disorders

Uncommon bradycardia, chest pain, palpitations (as part of withdrawal syndrome), ST depression, supraventricular tachycardia

Ear and labyrinth disorders

Uncommon tinnitus, vertigo

Eye disorders

Uncommon miosis, visual impairment

Gastrointestinal disorders
Very common nausea, vomiting, constipation
Common abdominal pain, diarrhoea, dry mouth, dyspepsia, gastritis, hiccup
Uncommon colic, dental caries, dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, stomatitis, regurgitation, retching

General disorders and administration site conditions
Common asthenia, fatigue, chills, fever
Uncommon accidental injury, facial flushing, lymphadenopathy, malaise, muscular rigidity, neck pain, oedema, peripheral oedema, pain, thirst
Not known drug withdrawal syndrome neonatal, Opioid tolerance*, Opioid withdrawal syndrome*

Hepatobiliary disorders
Uncommon biliary spasm, cholestasis, hepatic enzyme increased

Immune system disorders

Uncommon allergic reaction, anaphylactic reaction, anaphylactoid reaction, hypersensitivity

Injury, poisoning and procedural complications
Uncommon medication struck in throat

Metabolism and nutrition disorders
Common decreased appetite
Uncommon increased appetite, dehydration, hyponatraemia

Nervous system disorders
Very common dizziness, headache, somnolence
Common faintness, sedation, twitching, tremor, lethargy
Uncommon amnesia, drowsiness, abnormal gait, convulsion, dysgeusia (taste perversion), hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, muscle contractions involuntary, paraesthesia, seizures, speech disorder, stupor, syncope
Not Known hyperalgesia

Psychiatric disorders
Common abnormal dreams, anxiety, confusional state, insomnia, nervousness, thinking abnormal, depression
Uncommon affect lability, agitation, disorientation, dysphoria, euphoric mood, hallucination, libido decreased, mood altered, restlessness
Not known aggression, drug dependence* (see *PRECAUTIONS*)

Renal and urinary disorders
Uncommon ureteric spasm, urinary abnormalities, urinary retention, urinary tract infection

Reproductive system and breast disorders
Uncommon amenorrhoea, erectile dysfunction, hypogonadism

Respiratory, thoracic and mediastinal disorders
Common bronchospasm, dyspnoea, pharyngitis, voice alteration
Uncommon respiratory depression, choking

Not known central sleep apnoea syndrome

Skin and subcutaneous tissue disorders
Very common pruritus
Common hyperhidrosis, rash
Uncommon dry skin, exfoliative dermatitis, urticaria and other skin rashes

Vascular disorders
Common orthostatic hypotension
Uncommon hypotension, migraine, vasodilatation

Key:

Very common (≥ 1/10)	*Common* (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)	*Rare* (≥ 1/10,000 to < 1/1000)
Very rare (< 1/10,000)	*Not known* (cannot be estimated from the available data)

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.

* 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.

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 *PRECAUTIONS*)

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 *PRECAUTIONS*)

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 *PRECAUTIONS*)

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 *OxyContin* 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.

Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI)(See *PRECAUTIONS*)
Adrenal insufficiency (See *PRECAUTIONS*)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypotha/amic-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 respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, hypotonia, cold and/or clammy skin, miosis (dilated if hypoxia is severe), and sometimes bradycardia, 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 *OxyContin* 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 patent 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 product information 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of 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).

CLINICAL TRIALS

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, *OxyContin* 20 mg tablets, but not 10 mg tablets, was statistically significant in pain reduction compared with placebo (text from OxyContin US Prescribing Information dated April 2013)

Pharmacokinetics 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 mean apparent half-life of *OxyContin* tablets is 6.5 hours and steady-state is achieved in about one day.

Release of oxycodone from *OxyContin* tablets is independent of pH under physiological conditions.

OxyContin tablets have an oral bioavailability comparable with immediate release oral oxycodone, but achieve maximal plasma concentrations at about five hours compared with 1-1.5 hours for immediate release oral oxycodone. Peak and trough concentrations of oxycodone from OxyContin tablets 10 mg administered 12-hourly are similar to those achieved from immediate release oxycodone 5 mg administered 6-hourly.

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC).

Following ingestion of a high fat meal, peak plasma concentrations may be increased relative to dosing in the fasting state particularly with the higher doses. To minimise potential variability in peak concentrations if interchangeably administered with or without food, it is important that patients take the medication in a consistent manner in relation to the timing of meals.

OxyContin should either always be taken in a fasted state, or always with or just after food, usually with the same standard size of food each time.

Distribution

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

Metabolism

Oxycodoneis metabolised in the liver to form noroxycodone, oxymorphone, noroxymorphone, 6 α and β oxycodol and conjugated glucuronides. CYP3A4 and CYP2D6 are involved in the formation of noroxycodone and oxymorphone, respectively (see **INTERACTIONS WITH OTHER MEDICINES**). The contribution of these metabolites to the analgesic effect is insignificant.

Elimination

Oxycodone has an elimination half-life of between 3 - 5 hours, or approximately 4.5 hours. The plasma concentrations are only minimally affected by age, being 15% greater in the elderly compared with young subjects.

Patients with mild to severe hepatic or renal dysfunction may have an increase in elimination half-life compared with normal subjects, and therefore, may have higher plasma concentrations

of oxycodone and noroxycodone, and lower concentrations of oxymorphone compared with normal subjects. This may be accompanied by an increase in drug effects.

PRECLINICAL SAFETY DATA

Genotoxicity

Oxycodone was not genotoxic in bacterial gene mutation assays but was positive in the mouse lymphoma assay. In assays of chromosomal damage, genotoxic effects occurred in the human lymphocyte chromosomal aberration assay *in vitro,* but not in the *in vivo* bone marrow micronucleus assay in mice.

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 (equivalent to 6.8 mg/day in men and 24.6 mg/day in women, based on estimated AUC values). The doses were limited by opioid-related pharmacological effects of oxycodone.

PRESENTATION AND STORAGE CONDITIONS

Presentation

OxyContin® modified release tablets are round, unscored bi-convex tablets embossed with letters and numerals and contain the following quantities of oxycodone hydrochloride:
OxyContin® 10 mg contains oxycodone hydrochloride 10 mg (white, embossed with OP on one side and 10 on the other)
OxyContin® 20 mg contains oxycodone hydrochloride 20 mg (pink, embossed with OP on one side and 20 on the other)

Strengths and Pack sizes available in Malaysia:
10 mg – 20's and 30 tablets in blister packs
20 mg – 20's, 28's and 30 tablets in blister packs

Storage Conditions

Store below 30ºC.

NAME AND ADDRESS OF THE PRODUCT REGISTRATION HOLDER

DKSH MALAYSIA SDN BHD
B-11-01, The Ascent, Paradigm,
No. 1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya,
Selangor, Malaysia.

NAME AND ADDRESS OF MANUFACTURER

Knoa Pharmaceuticals LLC,
4701 International Blvd W, Wilson, NC
27893, USA

DATE OF MOST RECENT AMENDMENT

May 2026

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