PACKAGE INSERT
NAME OF THE MEDICINAL PRODUCT
(QUALITATIVE AND QUANTITATIVE COMPOSITION)

OxyContin® Neo 10 mg (oxycodone hydrochloride) Controlled-Release Tablets
(oxycodone hydrochloride 10 mg equivalent to 9 mg oxycodone base)

OxyContin® Neo 20 mg (oxycodone hydrochloride) Controlled-Release Tablets
(oxycodone hydrochloride 20 mg equivalent to 18 mg oxycodone base)

OxyContin® Neo 40 mg (oxycodone hydrochloride) Controlled-Release Tablets
(oxycodone hydrochloride 40 mg equivalent to 36 mg oxycodone base)

OxyContin® Neo 60 mg (oxycodone hydrochloride) Controlled-Release Tablets
(oxycodone hydrochloride 60 mg equivalent to 54 mg oxycodone base)

OxyContin® Neo 80 mg (oxycodone hydrochloride) Controlled-Release Tablets
(oxycodone hydrochloride 80 mg equivalent to 72 mg oxycodone base)

DOSAGE FORMS AND STRENGTHS
10 mg film-coated tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
20 mg film-coated tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
40 mg film-coated tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
60 mg film-coated tablets* (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
80 mg film-coated tablets* (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)
* 60 mg and 80 mg tablets for use in opioid-tolerant patients only

Indications and usage
OxyContin® Neo is indicated for the management of pain severe enough to require daily, around the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve ***OxyContin® Neo*** for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- ***OxyContin® Neo*** is not indicated as an as-needed (prn) analgesic

Dosage and administration

1. Initial Dosing
OxyContin® Neo should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OxyContin® Neo 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with ***OxyContin® Neo*** [see Warnings

and Precautions].

OxyContin® Neo tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving ***OxyContin® Neo*** tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death [see Warnings and Precautions].

Use of ***OxyContin® Neo*** as the First Opioid Analgesic
Initiate treatment with ***OxyContin® Neo*** with one 10 mg tablet orally every 12 hours.

Use of ***OxyContin® Neo*** in Patients who are not Opioid Tolerant
The starting dose for patients who are not opioid tolerant is ***OxyContin® Neo*** 10 mg orally every 12 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.
Conversion from other Oral Oxycodone Formulations to ***OxyContin® Neo***
Patients receiving other oral oxycodone formulations may be converted to ***OxyContin® Neo*** by administering one-half of the patient's total daily oral oxycodone dose as ***OxyContin® Neo*** every 12 hours.

Conversion from other Opioids to ***OxyContin® Neo***
Discontinue all other around-the-clock opioid drugs when ***OxyContin® Neo*** therapy is initiated.

There are no established conversion ratios for conversion from other opioids to ***OxyContin® Neo*** defined by clinical trials. Discontinue all other around-the-clock opioid drugs when ***OxyContin® Neo*** therapy is initiated and initiate dosing using ***OxyContin® Neo*** 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone requirements which could result in adverse reactions. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products.

Conversion from Methadone to ***OxyContin® Neo***
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to ***OxyContin® Neo***
Eighteen hours following the removal of the transdermal fentanyl patch, ***OxyContin® Neo*** treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg every 12 hours of ***OxyContin® Neo*****,** should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to ***OxyContin® Neo***, as there is limited documented experience with this conversion.

2. Titration and Maintenance of Therapy
Individually titrate ***OxyContin® Neo*** to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ***OxyContin® Neo*** to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse and misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of ***OxyContin® Neo*** or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the ***OxyContin® Neo*** dose. Because steady-state plasma concentrations are approximated in 1 day, ***OxyContin® Neo*** dosage may be adjusted every 1 to 2 days. If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

3. Patients with Hepatic Impairment
For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration [see **Clinical Pharmacology**].

4. Discontinuation of ***OxyContin® Neo***
When the patient no longer requires therapy with ***OxyContin® Neo*** tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue ***OxyContin® Neo***.

5. Administration of **OxyContin® Neo** tablets
Instruct patients to swallow ***OxyContin® Neo*** tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone **[**see **Warnings and Precautions].**

Instruct patients to take ***OxyContin® Neo*** one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth **[**see **Warnings and Precautions].**

Contraindications

Hypersensitivity to opioids and to any of the constituents or in any situation where opioids are contraindicated, acute respiratory depression, cor pulmonale, cardiac arrhythmias, severe bronchial asthma, chronic obstructive airways disease, paralytic ileus, suspected surgical abdomen, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance < 10ml/min) ,delayed gastric emptying, acute alcoholism, brain tumor, increased cerebrospinal or intracranial pressure, head injury, severe CNS depression, convulsive disorders, delirium tremens, hypercarbia, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Warnings and Precautions

1. Addiction, Abuse, and Misuse
OxyContin® Neo contains oxycodone. As an opioid, ***OxyContin® Neo*** exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence]. Because extended-release products such as ***OxyContin® Neo*** deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present **[see Drug Abuse and Dependence].**

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ***OxyContin® Neo*.** Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse or misuse prior to prescribing ***OxyContin® Neo***, and monitor all patients receiving ***OxyContin® Neo*** for the development of these behaviors and conditions. 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 potential for these risks should not, however, prevent the proper management of pain in any given

patient. Patients at increased risk may be prescribed opioids such as ***OxyContin® Neo*****,** but use in such patients necessitates intensive counseling about the risks and proper use of ***OxyContin® Neo*** along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse, or misuse of ***OxyContin® Neo*** by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death **[see Overdosage].**

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ***OxyContin® Neo*****.** Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug

2. Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see Overdosage]. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ***OxyContin® Neo*****,** the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression especially within the first 24-72 hours of initiating therapy with and following dosage increases of ***OxyContin® Neo***.

To reduce the risk of respiratory depression, proper dosing and titration of ***OxyContin® Neo*** are essential **[see Dosage and Administration].** Overestimating the ***OxyContin® Neo*** dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of ***OxyContin® Neo***, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper (see Dosage and Administration).

3. Neonatal Opioid Withdrawal Syndrome
Prolonged use of ***OxyContin® Neo*** during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

4. Risks of Concomitant Use of Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
Concomitant use of ***OxyContin® Neo*** with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g. erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g. ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of ***OxyContin® Neo*** is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in ***OxyContin® Neo***-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using ***OxyContin® Neo*** with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ***OxyContin® Neo*** -treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ***OxyContin® Neo*** until stable drug effects are achieved.

Concomitant use of ***OxyContin® Neo*** with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease

oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using ***OxyContin® Neo*** with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur.

5. Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma and death may result if ***OxyContin® Neo*** is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-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.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ***OxyContin® Neo*** 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.

6. Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of ***OxyContin® Neo*** in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: ***OxyContin® Neo***-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ***OxyContin® Neo***.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating ***OxyContin® Neo*** and when ***OxyContin® Neo*** is given concomitantly with other drugs that depress respiration [see **Warnings and Precautions**]. Alternatively, consider the use of non-opioids analgesics in these patients.

7. 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, anorexia, 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 doses 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.

8. Severe Hypotension

OxyContin® Neo may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see **Drug Interactions**]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ***OxyContin® Neo***. In patients with circulatory shock, ***OxyContin® Neo*** may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ***OxyContin® Neo*** in patients with circulatory shock.

9. Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness

In patients taking ***OxyContin® Neo*** who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) ***OxyContin® Neo*** may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ***OxyContin® Neo***. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ***OxyContin® Neo*** in patients with impaired consciousness or coma.

10. Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing ***OxyContin® Neo*** tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet ***OxyContin® Neo*** tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

11. Risk of Use in Patients with Gastrointestinal Conditions

OxyContin® Neo is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The oxycodone in ***OxyContin® Neo*** may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

12. Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in ***OxyContin® Neo*** may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during ***OxyContin® Neo*** therapy.

13. Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (e.g. pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g. buprenorphine) analgesics in patients who have are receiving a full opioid agonist analgesic, including ***OxyContin® Neo***. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Do not abruptly discontinue ***OxyContin® Neo in a patient physically dependent on opioids***. When discontinuing ***OxyContin® Neo*** in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain (see Dosage and Administration and Addiction, Abuse and misuse).

14. Risks of Driving and Operating Machinery

OxyContin® Neo may impair the mental or physical abilities needed to perform potentially hazardous activities such as

driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ***OxyContin® Neo*** and know how they will react to the medication.

15. Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

Adverse Reaction	**OxyContin (n=227)**	**Placebo (n=45)**
	(%)	**(%)**
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

- Addiction, Abuse, and Misuse [see Warnings and Precautions]
- Life-Threatening Respiratory depression [see Warnings and Precautions]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions]
- Interactions with Benzodiazepines and other CNS Depressants [see Warnings and Precautions]
- Adrenal Insufficiency [see Warnings and Precautions]
- Severe Hypotension [see Warnings and Precautions]
- GastrointestinalAdverse Reactions [see Warnings and Precautions]
- Seizures [see Warnings and Precautions]
- Withdrawal [see Warnings and Precautions]

1. Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ***OxyContin® Neo*** was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received ***OxyContin® Neo*** in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OxyContin® Neo may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock [see **Overdosage**].

The most common adverse reactions (>5%) reported by patients in clinical trials comparing ***OxyContin® Neo*** with placebo are shown in Table 1 below:

TABLE 1: Common Adverse Reactions (>5%)

In clinical trials, the following adverse reactions were reported in patients treated with ***OxyContin® Neo*** with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis

General disorders and administration site conditions: chills, fever
Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension
The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy
Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

2. Postmarketing Experience
The following adverse reactions have been identified during post-approval use of extended-release oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ***OxyContin® Neo***.
Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids

DRUG INTERACTIONS
TABLE 2: Clinically Significant Drug Interactions with *OxyContin® Neo*

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of ***OxyContin® Neo*** and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of ***OxyContin® Neo*** and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of ***OxyContin® Neo*** is achieved *[see Warnings and Precautions]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of ***OxyContin® Neo*** until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the ***OxyContin® Neo*** dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of ***OxyContin® Neo*** and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the ***OxyContin® Neo*** dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ***OxyContin® Neo*** dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Dosage and Administration, Warnings and Precautions]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ***OxyContin® Neo*** if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs

	that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions].*
Intervention:	The use of ***OxyContin® Neo*** is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of ***OxyContin® Neo*** and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ***OxyContin® Neo*** and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when ***OxyContin® Neo*** is used concomitantly with anticholinergic drugs.
Antihypertensive agent	

Clinical Impact:	Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.
Coumarin derivatives	
Clinical Impact:	Although there is little substantiating evidence, opiate agonists have been reported to potentiate the anticoagulant activity of coumarin derivatives.
Metoclopramide	
Clinical Impact:	Concurrent use with oxycodone may antagonise the effects of metoclopramide on gastrointestinal motility.

USE IN SPECIFIC POPULATIONS

1. Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. There are no available data with ***OxyContin® Neo*** in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 60 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Observe newborns for symptoms of neonatal opioid withdrawal and syndrome and manage accordingly.

2. Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. ***OxyContin® Neo*** is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including ***OxyContin® Neo*** can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However

this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Animal Data
Pregnant rats were treated with 0.5, 2, 4, and 8 mg/kg oxycodone hydrochloride (0.08, 0.3, 0.7, and 1.3 times the human daily dose of 60 mg/day, respectively based on a mg/m2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 1.3 times the human dose of 60 mg/day. The high dose produced maternal toxicity characterized by excessive gnawing on forelimbs and decreased body weight gain.

Pregnant rabbits were treated with 1, 5, 25, and 125 mg/kg oxycodone hydrochloride (0.3, 2, 8, and 40 times the human daily dose of 60 mg/day, respectively, based on a mg/m2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 40 times the human dose of 60 mg/day. The 25 mg/kg and 125 mg/kg doses high doses produced maternal toxicity characterized by decreased food consumption and body weight gain.

Pregnant rats were treated with 0.5, 2, and 6 mg/kg oxycodone hydrochloride (0.08, 0.32, and 1 times the human daily dose of 60 mg/kg, respective, based on a mg/m2 basis, during the period of organogenesis through lactation. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 60 mg/day, on a mg/m2 basis). However, body weight of these pups recovered.

In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human oral dose of 60 mg/day on a mg/m2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m2 basis).

3. Lactation

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended–release oxycodone, including ***OxyContin® Neo***, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ***OxyContin® Neo***.

Clinical Considerations
Infants exposed to ***OxyContin® Neo*** through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

4. Females and males of Reproductive Potential 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.

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6. Geriatric Use
In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% [see **Clinical Pharmacology**]. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse

reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, dosage reduction in debilitated, non-opioid-tolerant patients is recommended.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ***OxyContin® Neo*** slowly in these patients and monitor closely for signs of central nervous system and respiratory depression.

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

6. Hepatic Impairment
A study of ***OxyContin® Neo*** in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function [see **Clinical Pharmacology**]. Therefore, a dosage reduction is recommended for these patients. Monitor closely for signs of respiratory depression, sedation, and hypotension.

7. Renal Impairment
In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation [see **Clinical Pharmacology**].

8. Sex Differences
In pharmacokinetic studies with ***OxyContin® Neo***, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

DRUG ABUSE AND DEPENDENCE
OxyContin® Neo contains oxycodone, a Schedule II controlled substance.

1. Abuse
OxyContin® Neo contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, and oxymorphone and tapentadol. ***OxyContin® Neo*** can be abused and is subject to misuse, addiction, and criminal diversion [see **Warnings and Precautions**].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use with disorders. Drug-seeking tactics include

emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated 'loss' of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction.
Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OxyContin® Neo, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of ***OxyContin® Neo***
OxyContin® Neo is for oral use only. Abuse of ***OxyContin® Neo*** poses a risk of overdose and death. The risk is increased with concurrent use of ***OxyContin® Neo*** with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved ***OxyContin® Neo*** enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in ***OxyContin® Neo*** can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies
OxyContin® Neo is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of ***OxyContin® Neo*** resulting from a change in formulation, in this section, the original formulation of ***OxyContin®***, which is no longer marketed, will be referred to as "original ***OxyContin®*** " and the reformulated, currently marketed product will be referred to as ***OxyContin® Neo***.

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original ***OxyContin® Neo***, there is an increase in the ability of ***OxyContin® Neo*** to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for ***OxyContin® Neo*** relative to an immediate-release oxycodone. When subjected to an aqueous environment, ***OxyContin® Neo*** gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies
In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed ***OxyContin® Neo*** 30 mg tablets, coarsely crushed ***OxyContin® Neo*** 30 mg tablets, finely crushed original ***OxyContin® Neo*** 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed ***OxyContin® Neo***, finely crushed original ***OxyContin® Neo***, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n=10) of subjects with finely crushed ***OxyContin® Neo***, compared with 7% (n=2) of subjects with finely crushed original ***OxyContin®*** and no subjects with powdered oxycodone HCl.
The intranasal administration of finely crushed ***OxyContin® Neo*** was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original ***OxyContin®*** or powdered oxycodone HCl as summarized in Table 2.

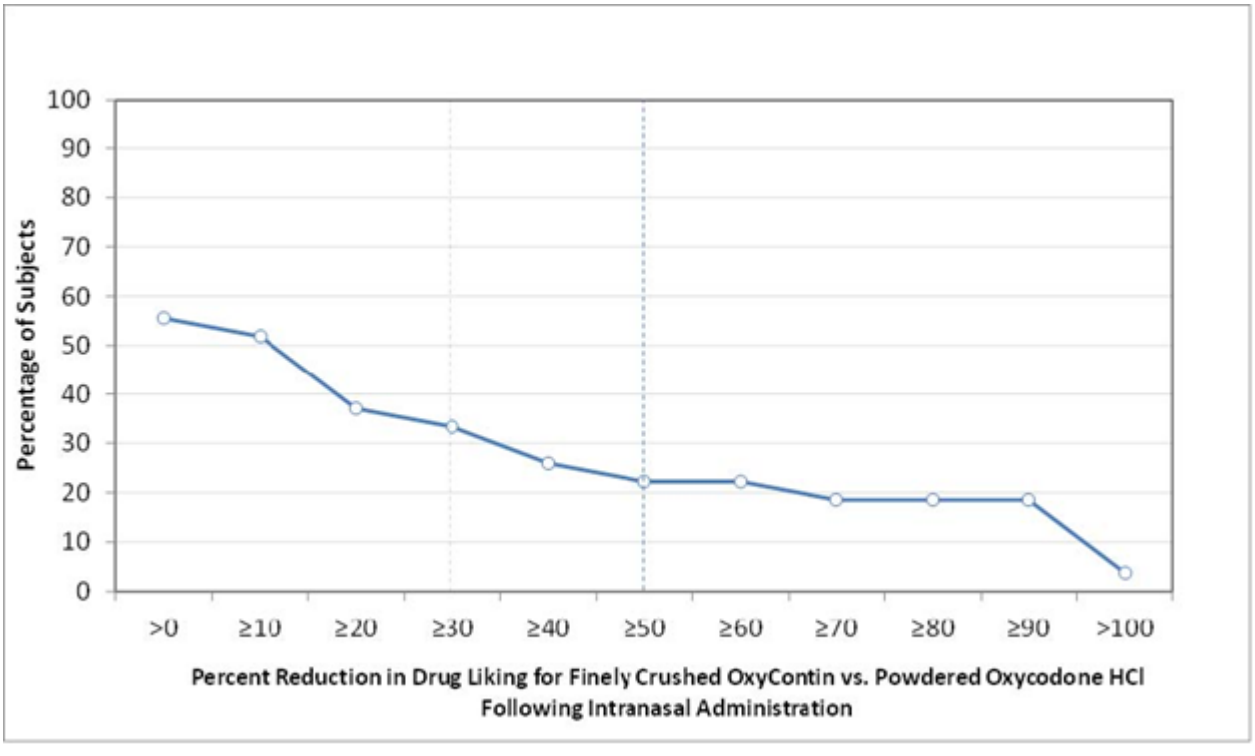
Table 2: Summary of Maximum Drug Liking (Emax) Data Following Intranasal Administration

VAS Scale (100 mm)*		***OxyContin® Neo*** (finely crushed)	Original ***OxyContin®*** (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed ***OxyContin® Neo*** compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for ***OxyContin® Neo*** vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with ***OxyContin® Neo*** relative to oxycodone
HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with ***OxyContin® Neo*** relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with ***OxyContin® Neo*** compared to oxycodone HCl, and approximately 22% (n= 6) of subjects had a reduction of at least 50% in drug liking with ***OxyContin® Neo*** compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for *OxyContin® Neo* vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed ***OxyContin® Neo*** relative to finely crushed original ***OxyContin®*** were comparable to the results of finely crushed ***OxyContin® Neo*** relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with ***OxyContin® Neo*** relative to original ***OxyContin®***. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n= 8) of subjects had a reduction of at least 50% in drug liking with ***OxyContin® Neo*** compared to original ***OxyContin®***.

Summary

The *in vitro* data demonstrate that ***OxyContin® Neo*** has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that ***OxyContin® Neo*** has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of ***OxyContin® Neo*** by these routes, as well as by the oral route is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of ***OxyContin® Neo*** on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OxyContin® Neo contains oxycodone, an opioid agonist with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. ***OxyContin® Neo*** can be

abused and is subject to misuse, addiction, and criminal diversion **[See Warnings and Precautions, and Drug Abuse and Dependence].**

3. Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) or mixed agonist/antagonist analgesics (e.g. pentazocine, butorphanol, nalbuphine) or partial agonists (e.g. buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OxyContin® Neo should not be abruptly discontinued [see **Dosage and Administration**]. If ***OxyContin® Neo*** is abruptly discontinued in a physically-dependent patient, withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see **Use in Specific Populations**].

OVERDOSAGE

Clinical Presentation

Acute overdosage with ***OxyContin® Neo*** can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

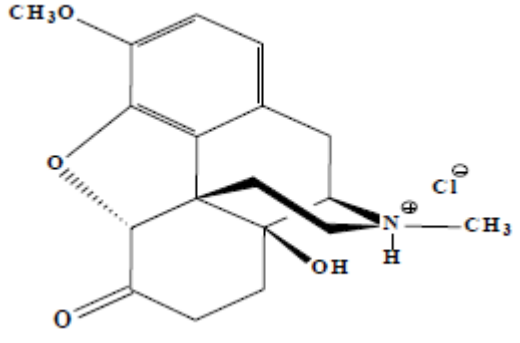
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal is expected to be less than the duration of action of oxycodone in ***OxyContin® Neo***, carefully monitor the patient until spontaneous respiration is reliably reestablished. ***OxyContin® Neo*** will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonists is suboptimal or only brief in nature, administer, additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

Description

OxyContin® Neo (oxycodone hydrochloride controlled-release) is an opioid agonist supplied in 10 mg, 20 mg, 40 mg, 60 mg and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 20 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.
The 20 mg tablets also contain polysorbate 80 and red iron oxide.
The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.
The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.
The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

CLINICAL PHARMACOLOGY

1. Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesic. Like all full opioid agonists, there is no ceiling effect to analgesia for Oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

2. Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO_2 tension and electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia overdose situations [see **Overdosage**].

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, testosterone, and luteinizing hormone (LH) in humans. [See Adverse Reactions] They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective “drug effect”, analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been

previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance. [see **Dosage and Administration**]

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

The dose of ***OxyContin® Neo*** must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients [see **Dosage and Administration**].

3. Pharmacokinetics

The activity of ***OxyContin® Neo*** is primarily due to the parent drug oxycodone. ***OxyContin® Neo*** is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving ***OxyContin® Neo*** impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from ***OxyContin® Neo*** is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from ***OxyContin® Neo*** to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with ***OxyContin® Neo*** in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life (t½) of oxycodone following the administration of ***OxyContin® Neo*** was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for ***OxyContin® Neo*** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (Cmax) and extent of absorption (AUC) (see Table 2). Given the short elimination t½ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with ***OxyContin® Neo***. In a study comparing 10 mg of ***OxyContin® Neo*** every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and Cmax, and similar for Cmin (trough) concentrations.

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	Tmax (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

TABLE 3
Mean [% coefficient of variation]
* for single-dose AUC = $AUC_{0\text{-}inf}$
†data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from ***OxyContin® Neo***.

Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk [see **Use in Specific Populations**].

Elimination

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs [see **Drug Interactions**].

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Special Populations

Geriatric Population

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Sex
Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown [see **Use in Specific Populations**].

Renal Impairment
Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination t½ for oxycodone of 1 hour.

Hepatic Impairment
Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination t½ for oxycodone increased by 2.3 hours.

Drug-Drug Interactions
CYP3A4 Inhibitors
CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of ***OxyContin® Neo*** (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and Cmax by 170% and 100%, respectively [see **Drug Interactions**].

CYP3A4 Inducers
A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and Cmax values by 86% and 63%, respectively [see **Drug Interactions**].

CYP2D6 Inhibitors
Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with ***OxyContin® Neo*** [see **Drug Interactions**].

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Mutagenesis
Oxycodone was genotoxic in the mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay , the in vitro bacterial reverse mutation assay (Ames test and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility
In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (up to 8 mg/kg/day), up to 1.3 times a human dose of 60mg/day.

CLINICAL STUDIES
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, but not 10 mg, was statistically significant in pain reduction compared with placebo.

HOW SUPPLIED/STORAGE AND HANDLING

OxyContin® Neo (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 30 and 12, and unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton.

OxyContin® Neo (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 30 and 12, and unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton.

OxyContin® Neo (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 30 and 12, and unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton.

OxyContin® Neo (oxycodone hydrochloride controlled-release) Tablets 60 mg are round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 30 and 12, and unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton.

OxyContin® Neo (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 30 and 12, and unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton.

Store at or below 30°C
Dispense in tight, light-resistant, child-resistant closure, opaque plastic bottles
or
Dispense unit dose packaging with 10 individually numbered tablets per card; three cards per glue end carton, two cards per glue end carton and one card per glue end carton

Shelf life
Refer to the manufacture and expiry date shown on the blister and carton

MARKETING AUTHORISATION HOLDER
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