

# PRODUCT MONOGRAPH

## <sup>N</sup>RAN™-OXYCODONE CR

Oxycodone Hydrochloride Controlled Release Tablets

15 mg, 20 mg, 40 mg, 60 mg and 80 mg oxycodone hydrochloride

Manufacturer's Standard

Opioid Analgesic

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# <sup>N</sup>RAN™ OXYCODONE CR

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Controlled Release Tablets/ 15 mg, 20 mg, 40 mg, 60 mg, 80 mg	<b>Tablets:</b> colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, povidone. <b>Tablet coating:</b> D&C Yellow No.10 Aluminum Lake (for 80 mg tablet), FD&C Blue No.2 (for 15 mg and 80 mg tablet), FD&C Red No.40 ( for 60 mg tablet), FD&C Yellow No.5 (for 40 mg tablet), FD&C Yellow No 6 (for 60 mg tablet), iron oxide ((black, yellow) for 15 mg tablet), iron oxide ((red, yellow) for 20 mg tablet), iron oxide ((yellow) for 40 mg tablet), talc (for 20 mg, 40 mg and 80 mg tablet), titanium dioxide, hypromellose, macrogol.

### INDICATIONS AND CLINICAL USE

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets are indicated for relief of moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more.

### CONTRAINDICATIONS

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets are contraindicated for:

- Patients who are hypersensitive to the active substance (oxycodone) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).

- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute asthma or other obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### **POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE (SEE WARNINGS AND PRECAUTIONS - PATIENT COUNSELLING INFORMATION)**

- **RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets must be swallowed whole. Taking cut, broken, chewed, dissolved or crushed RAN-OXYCODONE CR tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.**
- **Use in Drug and Alcohol Addiction**  
RAN-OXYCODONE CR is an opioid with no approved use in the management of addictive disorders. Their proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.
- **Abuse of Opioid Formulations**  
RAN-OXYCODONE CR is intended for oral use only.  
Abuse can lead to overdose and death. This risk is increased when the tablets are cut, crushed, broken, dissolved or chewed, and with concurrent consumption of alcohol or other CNS depressants. With parenteral abuse, the tablet excipients, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.
- **RAN-OXYCODONE CR 60 mg and 80 mg tablets, or a single dose greater than 40 mg, are for use in opioid tolerant patients only (see also DOSAGE AND ADMINISTRATION). A single dose greater than 40 mg, or total daily doses greater**

than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids (see **PRECAUTIONS, Drug Interactions**).

- **Patients should be instructed not to give RAN-OXYCODONE CR to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.**

Patients should be cautioned not to consume alcohol while taking RAN-OXYCODONE CR, as it may increase the chance of experiencing dangerous side effects.

### **Carcinogenesis and Mutagenesis**

See **TOXICOLOGY** section.

### **Cardiovascular**

**Hypotension:** Oxycodone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

### **Dependence/Tolerance**

As with other opioids, tolerance and physical dependence may develop upon repeated administration of oxycodone and there is a potential for development of psychological dependence. RAN-OXYCODONE CR tablets should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential.

Abuse and addiction are separate and distinct from physical dependence and tolerance. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Addiction is not usually a problem in patients with pain in whom opioid analgesics are appropriately indicated. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Opioids, such as oxycodone, should be used with particular care in patients with a history of alcohol and drug abuse.

Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist (see **ADVERSE REACTIONS**, Withdrawal (Abstinence) Syndrome).

Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

### **Gastrointestinal Effects**

**Acute Abdominal Conditions:** Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Oxycodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

### **Neurologic**

**CNS Depression:** Oxycodone should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants, including alcohol. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored (see **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

**Head Injury:** The respiratory depressant effects of oxycodone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, oxycodone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, oxycodone must be used with extreme caution and only if it is judged essential

### **Peri-Operative Considerations:**

RAN-OXYCODONE CR is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with RAN-OXYCODONE CR for at least 24 hours before the operation and RAN-OXYCODONE CR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if RAN-OXYCODONE CR is to be continued after the patient recovers from the postoperative period, a new dosage should be administered in accordance with the

changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Oxycodone and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

RAN-OXYCODONE CR should not be used in the early post-operative period (12-24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

### **Psychomotor Impairment**

**Driving and Operating Dangerous Machinery:** Oxycodone may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of oxycodone with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

### **Respiratory**

**Respiratory Depression:** Oxycodone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide (CO<sub>2</sub>) on the respiratory centre and the respiratory depressant effects of oxycodone may reduce respiratory drive to the point of apnea.

### **Patient Counselling Information:**

A patient information sheet should be provided when RAN-OXYCODONE CR tablets are dispensed to the patient.

Patients receiving RAN-OXYCODONE CR should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal consequences.
2. Patients should be advised that RAN-OXYCODONE CR contains oxycodone, an opioid pain medicine.

3. Patients should be advised that RAN-OXYCODONE CR should only be taken as directed. The dose of RAN-OXYCODONE CR should not be adjusted without consulting with a physician.
4. RAN-OXYCODONE CR must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal oxycodone overdose.
5. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should not combine RAN-OXYCODONE CR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with RAN-OXYCODONE CR.
8. Patients should be advised that if they have been receiving treatment with RAN-OXYCODONE CR and cessation of therapy is indicated, it may be appropriate to taper RAN-OXYCODONE CR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms (see ADVERSE REACTIONS, Withdrawal (Abstinence) Syndrome).
9. Patients should be advised that the most common adverse reactions that may occur while taking RAN-OXYCODONE CR are asthenia, constipation, dizziness, dry mouth, headache, nausea, pruritus, somnolence, sweating and vomiting.
10. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
11. Patients should be advised that RAN-OXYCODONE CR may cause drowsiness, dizziness or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on RAN-OXYCODONE CR or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of RAN-OXYCODONE CR.
12. Patients should be advised that RAN-OXYCODONE CR is a potential drug of abuse. They should protect it from theft or misuse.
13. Patients should be advised that RAN-OXYCODONE CR should never be given to anyone other than the individual for whom it was prescribed.

14. Patients should be advised that RAN-OXYCODONE CR 60 and 80 mg tablets or a single dose greater than 40 mg are for use only in individuals tolerant to the effect of opioids.
15. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with RAN-OXYCODONE CR. Women who are breastfeeding or pregnant should not use RAN-OXYCODONE CR.

### **Special Populations**

**Special Risk Groups:** Oxycodone should be administered with caution to patients with a history of alcohol and drug abuse, and in a reduced dosage to debilitated patients, patients with severely reduced hepatic or renal function, and in patients with Addison's disease, myxedema, hypothyroidism, toxic psychosis, pancreatitis, prostatic hypertrophy or urethral stricture.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. Plasma concentrations of oxycodone are increased by approximately 15% in elderly subjects receiving oxycodone hydrochloride; by 50 - 60% in patients with moderate degrees of renal impairment; and by approximately two-fold in patients with hepatic cirrhosis.

**Pregnant Women:** Animal reproduction studies have revealed no evidence of harm to the fetus due to oxycodone. In humans, it has not conclusively been established whether oxycodone can cause fetal harm when administered during pregnancy or if it can affect reproductive capacity, therefore, RAN-OXYCODONE CR is contraindicated in patients who are pregnant.

**Labour, Delivery and Nursing Women:** In view of the potential for opioids to cross the placental barrier and to be excreted in breast milk, RAN-OXYCODONE CR is contraindicated during labour or in nursing mothers. Physical dependence or respiratory depression may occur in the infant if opioids are administered during labour.

### **“In Vitro” Dissolution Studies of Interaction with Alcohol**

Increasing concentrations of alcohol in the dissolution medium resulted in a slight decrease in the rate of release of oxycodone from oxycodone hydrochloride tablets.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse effects of oxycodone hydrochloride controlled release tablets are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of oxycodone hydrochloride are asthenia, constipation, dizziness, dry mouth, headache, nausea, pruritus, somnolence, sweating and vomiting.

**Sedation:** Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

**Nausea and Vomiting:** Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumour invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

**Constipation:** Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required.

The following adverse effects occur less frequently with opioid analgesics and include those reported in oxycodone hydrochloride clinical trials, whether related or not to oxycodone.

*General and CNS:* abnormal dreams, abnormal gait, agitation, amnesia, anaphylactic reaction, anaphylactoid reaction, anxiety, confusional state, convulsion, delirium, depersonalization, depression, disorientation, drug dependence, drug tolerance, drug withdrawal syndrome, dysphoria, edema peripheral, emotional lability, euphoria, hallucinations, headache, hypertonia, hypoaesthesia, hypotonia,

	insomnia, miosis, muscle contractions involuntary, nervousness, paresthesia, speech disorder, thought abnormalities, tinnitus, tremor, twitching, vertigo and vision abnormalities
<i>Cardiovascular:</i>	chest pain, faintness, hypotension, migraine, orthostatic hypertension, palpitation, ST depression, syncope, tachycardia and vasodilation
<i>Respiratory:</i>	bronchitis, bronchospasm, cough, dyspnea, pharyngitis, pneumonia, respiratory depression, sinusitis and yawning
<i>Gastrointestinal:</i>	abdominal pain, anorexia, biliary spasm, cholestasis, dental caries, diarrhea, dyspepsia, dysphagia, eructation, flatulence, gastritis, gastrointestinal disorder, hiccups, ileus, increased appetite, stomatitis and taste perversion
<i>Genitourinary:</i>	amenorrhea, antidiuretic effects, libido decreased, dysuria, hematuria, impotence, polyuria, urinary retention or hesitancy
<i>Dermatologic:</i>	dry skin, exfoliative dermatitis, edema, other skin rashes and urticaria
<i>Other:</i>	allergic reaction, asthenia, chills, dehydration, fever, hypoglycemia, increased hepatic enzymes, lymphadenopathy, malaise, thirst and weight loss

**Withdrawal (Abstinence) Syndrome:** Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

## **DRUG INTERACTIONS**

### **Overview**

CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, antidepressants, sleeping aids, phenothiazines, neuroleptics, chloral hydrate and glutethimide may enhance the depressant effect of oxycodone.

Oxycodone should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are currently receiving other central nervous system depressants. Monoamine oxidase inhibitors (including procarbazine hydrochloride), pyrazolidone, antihistamines, beta-blockers and alcohol may also enhance the depressant effect of oxycodone.

Oxycodone is metabolized in part by cytochrome CYP 2D6 and cytochrome CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various coadministered drugs, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly.

### **Drug-Drug Interactions**

#### *Inhibitors of CYP3A4:*

Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone hydrochloride, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and  $C_{max}$  by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with RAN-OXYCODONE CR is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

#### *Inducers of CYP3A4:*

CYP450 inducers, such as rifampin, carbamazepine and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, the development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and  $C_{max}$  by 86% and 63% respectively. If coadministration with RAN-OXYCODONE CR is necessary, caution is advised when initiating therapy with, currently taking or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

#### *Inhibitors of CYP2D6:*

Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not been shown to be of clinical significance during oxycodone treatment.

#### *Administration with Mixed Activity Agonist/Antagonist Opioids*

Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

### *MAO Inhibitors*

MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. RAN-OXYCODONE CR is contraindicated in patients receiving MAO Inhibitors or who have used them within the previous 14 days (see **CONTRAINDICATIONS**).

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

**RAN-OXYCODONE CR tablets should be swallowed whole and should not be cut, broken, chewed, dissolved or crushed since this can lead to rapid release and absorption of a potentially fatal dose of oxycodone.**

**RAN-OXYCODONE CR 60 and 80 mg tablets, or a single dose greater than 40 mg, are for use in opioid tolerant patients only. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.**

RAN-OXYCODONE CR should not be used in the early post-operative period (12 - 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

RAN-OXYCODONE CR not indicated for rectal administration.

The controlled release tablets may be taken with or without food, with a glass of water.

### **Recommended Dose and Dosage Adjustment**

**Adults:** Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.

**Patients Not Receiving Opioids at the Time of Initiation of Oxycodone Treatment:** The usual initial adult dose of Oxycodone Hydrochloride Controlled Release Tablets for patients who have not previously received opioid analgesics is 10\* or 20 mg every 12 hours.

\* RAN-OXYCODONE CR is NOT available as 10 mg controlled release tablets.

**Patients Currently Receiving Opioids:** Patients currently receiving other oral oxycodone formulations may be transferred to RAN-OXYCODONE CR tablets at the same total daily oxycodone dosage, equally divided into two 12 hourly RAN-OXYCODONE CR doses.

For patients who are receiving an alternate opioid, the "oral oxycodone equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. This total daily oral oxycodone dose should then be equally divided into two 12 hourly RAN-OXYCODONE CR doses. It is usually appropriate to treat a patient with only one opioid at a time.

**Table 1: Opioid Analgesics: Approximate Analgesic Equivalences<sup>1</sup>**

Drug	Equivalent Dose (mg) <sup>2</sup> (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
<b>Strong Opioid Agonists</b>			
Morphine	10	60 <sup>3</sup>	3-4
Oxycodone	15	30 <sup>4</sup>	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine <sup>6</sup>	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone <sup>5</sup>	-	-	-
Heroin	5-8	10-15	3-4
<b>Weak Opioid Agonists</b>			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
<b>Mixed Agonist-Antagonists<sup>7</sup></b>			
Pentazocine <sup>6</sup>	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

**References:**

- <sup>1</sup> Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.  
Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.  
Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.  
Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.
- <sup>2</sup> **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25-50% of the equianalgesic**

dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.<sup>†</sup> Upward titration may be required to reach appropriate maintenance doses.

<sup>†</sup>Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

<sup>3</sup> For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2 - 3: 1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

<sup>4</sup> Based on single entity oral oxycodone in acute pain.

<sup>5</sup> Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

<sup>6</sup> Not recommended for the management of chronic pain.

<sup>7</sup> Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Patients who are receiving 1 to 5 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine should be started on 10\* to 20 mg Oxycodone Hydrochloride Controlled Release Tablets q12h. For patients receiving 6 to 9 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 20 to 30 mg q12h should be used and for patients receiving 10 to 12 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, a starting dose of 30 to 40 mg q12h is suggested. For those receiving > 12 tablets/capsules per day of a fixed-dose combination opioid/non-opioid containing 5 mg of oxycodone or 30 mg codeine, conversions should be based on the total daily opioid dose.

\* RAN-OXYCODONE CR is NOT available as 10 mg controlled release tablets.

**Use with Non-Opioid Medications:** If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. RAN-OXYCODONE CR can be safely used concomitantly with usual doses of other non-opioid analgesics.

**Dose Titration:** Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of controlled release oxycodone (RAN-OXYCODONE CR) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response. In patients receiving RAN-OXYCODONE CR, the dose may be titrated at intervals of 24-36 hours to that which provides satisfactory pain relief without unmanageable side effects. RAN-OXYCODONE CR is designed to allow 12 hourly dosing.

**If pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release oxycodone (RAN-OXYCODONE CR).**

**Adjustment or Reduction of Dosage:** Following successful relief of pain, periodic attempts to reassess the opioid analgesic requirements should be made. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q12h RAN-OXYCODONE CR for the first two days, followed thereafter by a 25% reduction every two days.

Withdrawal symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with these types of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

### **Missed Dose**

If the patient forgets to take a dose, it should be taken as soon as possible, however, if it is almost time for the next scheduled dose, they should skip the missed dose and take their next dose at the scheduled time and in the normal amount.

## **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

**Symptoms:** Serious overdose with oxycodone may be characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miotic pupils, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Severe overdose may result in apnea, circulatory collapse, cardiac arrest and death.

**Treatment:** Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdose or as a result of unusual sensitivity to oxycodone. An appropriate dose of an

opioid antagonist should therefore be administered, preferably by the intravenous route. The usual initial i.v. adult dose of naloxone is 0.4 mg or higher. 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 to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In individuals physically dependent on opioids, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic 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.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release formulation has been taken.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Oxycodone is a semi-synthetic opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, oxycodone produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory center to CO<sub>2</sub>, nausea and vomiting via stimulation of the chemoreceptor trigger zone, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

### **Pharmacodynamics**

Oxycodone retains at least one-half of its analgesic activity when administered orally and with acute dosing is approximately twice as potent as orally administered morphine.

There is no intrinsic limit to the analgesic effect of oxycodone; like morphine, adequate doses will relieve even the most severe pain. Clinically however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

**Central Nervous System:** Oxycodone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO<sub>2</sub> tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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 in the setting of oxycodone overdose.

**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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

**Cardiovascular System:** Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

**Endocrine System:** Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifested from these hormonal changes.

**Immune System:** In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

### **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 papillary 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. As a result, patients must be treated with individualized titration of dosage to the desired effect. 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.

### **Concentration – Adverse Reaction Relationship**

There is a significant relationship between increasing oxycodone plasma concentrations 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 side effects.

The dose of RAN-OXYCODONE CR must be individualized (see **DOSAGE AND ADMINISTRATION**) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

### **Pharmacokinetics**

The activity of RAN-OXYCODONE CR is primarily due to the parent drug oxycodone. RAN-OXYCODONE CR is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving RAN-OXYCODONE CR impairs the controlled release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

### **Absorption**

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

### **Distribution**

Following intravenous administration, the steady-state volume of distribution (V<sub>ss</sub>) 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.

### **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 is present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent.

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 ( $\alpha$ - and  $\beta$ -oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration in to 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.

Pharmacokinetic studies of oxycodone hydrochloride controlled release tablets in normal volunteers demonstrate that both AUC and  $C_{max}$  increase in a dose proportional manner and that the six tablet strengths are bioequivalent. In single dose studies, oxycodone hydrochloride controlled release tablet was absorbed to an equivalent extent as immediate release oxycodone but with a reduced maximum concentration ( $C_{max}$  ratio approximately 50%), a prolonged (2.4x) time to maximum concentration ( $t_{max}$  approximately 2.8 hours), with a biphasic absorption pattern, with two apparent absorption half-times of 0.6 and 6.9 hours, which describe the initial release of oxycodone from the tablet, followed by a prolonged release. Release in vitro is pH-independent.

In steady state pharmacokinetic studies of oxycodone hydrochloride controlled release tablets q12h, maximum plasma concentrations ( $C_{max}$ ) of oxycodone were equivalent to those obtained with q6h administration of oral immediate release preparations and was achieved approximately 3 hours after administration of oxycodone hydrochloride controlled release tablets. Steady-state was achieved within 24-36 hours of initiation of dosing. The absorption of oxycodone from oxycodone hydrochloride controlled release tablets is not significantly influenced when administered in the presence of food.

### **STORAGE AND STABILITY**

Store RAN-OXYCODONE CR Tablets between 15° C and 30° C. Keep container tightly closed. Protect from moisture. Keep in cool, dry place.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets 15 mg are grey colored, round shaped, biconvex film-coated tablets, debossed with “**rbx**” on one side and “**OC15**” on the other side. They are available in bottles of 10 and 1000 tablets.

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets 20 mg are pink colored, round shaped, biconvex film-coated tablets, debossed with “**rbx**” on one side and “**OC20**” on the other side. They are available in bottles of 10 and 1000 tablets.

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets 40 mg are yellow colored, round shaped, biconvex film-coated tablets, debossed with “**rbx**” on one side and “**OC40**” on the other side. They are available in bottles of 10 and 1000 tablets.

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets 60 mg are red colored, round shaped, biconvex film-coated tablets, debossed with “**rbx**” on one side and “**OC60**” on the other side. They are available in bottles of 10 and 1000 tablets.

RAN-OXYCODONE CR (oxycodone hydrochloride) controlled release tablets 80 mg are green colored, capsule shaped, biconvex film-coated tablets, debossed with “**rbx**” on one side and “**OC80**” on the other side. They are available in bottles of 10 and 1000 tablets.

**Tablets:** colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, povidone.

**Tablet coating:** D&C Yellow No.10 Aluminum Lake (for 80 mg tablet), FD&C Blue No.2 (for 15 mg and 80 mg tablet), FD&C Red No.40 (for 60 mg tablet), FD&C Yellow No.5 (for 40 mg tablet), FD&C Yellow No 6 (for 60 mg tablet), iron oxide ((yellow) for 40 mg tablet), iron oxide ((black, yellow) for 15 mg tablet), iron oxide ((red, yellow) for 20 mg tablet), talc (for 20 mg, 40 mg and 80 mg tablet), titanium dioxide, hypromellose, macrogol.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Oxycodone hydrochloride is a semi-synthetic derivative of the naturally occurring opium alkaloid, thebaine.

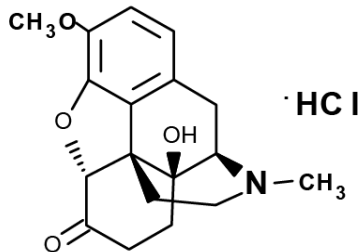
Proper name: Oxycodone Hydrochloride

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

Molecular formula:  $C_{18}H_{21}NO_4 \cdot HCl$

Molecular mass: 351.82 g/mol

Structural formula:



Physicochemical properties: Oxycodone hydrochloride is a white to off-white, odourless, hygroscopic crystals or powder. It is soluble in water and slightly soluble in alcohol and has a melting point of 218°C to 223°C.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, two-period, two-sequence, single-dose, crossover bioequivalence study comparing oxycodone hydrochloride controlled release tablets, 20 mg (Ranbaxy Pharmaceuticals Canada Inc.) with OxyContin<sup>®</sup> (oxycodone hydrochloride) controlled release tablets, 20 mg (Purdue Pharma Inc.) was conducted in healthy, adult subjects under fasting conditions. The data from the 23 subjects included in statistical analysis is presented below.

Oxycodone (1 x 20 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference <sup>†</sup>	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (ng.hr/mL)	220.63 231.55 (30.48)	217.71 227.29 (28.52)	101.34	94.29 - 108.92
AUC <sub>I</sub> (ng.hr/mL)	224.17 234.77 (29.95)	221.79 231.11 (28.13)	101.07	94.10 - 108.56
C <sub>max</sub> (ng/mL)	21.76 22.79 (32.88)	20.28 21.21 (29.74)	107.33	99.02 - 116.33
T <sub>max</sub> <sup>§</sup> (h)	4.50 (2.33 – 6.00)	3.00 (1.00 – 5.00)		
T <sub>½</sub> <sup>ε</sup> (h)	4.45 (12.59)	5.18 (16.72)		

\* Oxycodone Hydrochloride 20 mg Controlled Release Tablet, of Ranbaxy Pharmaceuticals Canada Inc.

† OxyContin<sup>®</sup> (oxycodone hydrochloride) controlled release tablet 20 mg (Purdue Pharma) were purchased in Canada.

§ Expressed as the Median (Range) only

ε Expressed as the Arithmetic Mean (CV%) only

A randomized, two-period, two-sequence, single-dose, crossover bioequivalence study comparing oxycodone hydrochloride controlled release tablets, 20 mg (Ranbaxy Pharmaceuticals Canada Inc.) with OxyContin® (oxycodone hydrochloride) controlled release tablets, 20 mg (Purdue Pharma Inc.) was conducted in healthy, adult subjects under non-fasting conditions. The data from the 24 subjects included in statistical analysis is presented below.

Oxycodone (1 x 20 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (ng·hr/mL)	243.08 252.67 (29.01)	251.51 262.67 (27.60)	96.65	91.67 – 101.89
AUC <sub>I</sub> (ng·hr/mL)	245.68 255.14 (28.74)	254.27 265.44 (27.48)	96.62	91.69 – 101.83
C <sub>max</sub> (ng/mL)	26.82 26.38 (33.75)	23.47 24.13 (22.03)	114.25	107.98 – 120.88
T <sub>max</sub> <sup>§</sup> (h)	5.00 (2.67-8.00)	3.84 (2.00-4.50)		
T <sub>1/2</sub> <sup>€</sup> (h)	4.32 (14.98)	4.83 (10.48)		

\* Oxycodone Hydrochloride 20 mg Controlled Release Tablet, of Ranbaxy Pharmaceuticals Canada Inc.

† OxyContin® (oxycodone hydrochloride) controlled release tablet 20 mg (Purdue Pharma) were purchased in Canada.

§ Expressed as the Median (Range) only

€ Expressed as the Arithmetic Mean (CV%) only

**Study No. R09-0968**

A blinded, single-dose, balanced, randomized, two treatment, two period, two sequence, crossover bioequivalence study of RAN-OXYCODONE CR Tablets 40 mg (Ranbaxy Pharmaceuticals Canada Inc.) compared to that of OxyContin<sup>®</sup> Tablets 40 mg by Purdue Pharma was conducted in 21 healthy, adult, human subjects under fasting conditions. A summary of the pharmacokinetic parameters is summarized in the table below:

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

Oxycodone (1 x 40 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference <sup>†</sup>	% Ratio of Geometric Least Square Means	90% Confidence Interval
AUC <sub>0-t</sub> (ng-hr/mL)	404.17 413.32 (22.64)	363.71 372.96 (25.24)	111.12	(105.12 - 117.47)
AUC <sub>0-inf</sub> (ng-hr/mL)	407.39 416.38 (22.42)	369.12 379.01 (25.21)	110.37	(104.25 - 116.84)
C <sub>max</sub> (ng/mL)	40.45 41.19 (23.46)	37.00 37.63 (21.56)	109.34	(102.38 - 116.78)
T <sub>max</sub> <sup>§</sup> (h)	3.83 (31.14)	2.39 (39.56)		
T <sub>1/2</sub> <sup>€</sup> (h)	4.72 (18.70)	5.97 (25.59)		

\* RAN-OXYCODONE CR tablets 40 mg (Ranbaxy Pharmaceuticals Canada Inc.)

<sup>†</sup> OxyContin<sup>®</sup> (oxycodone hydrochloride) controlled release tablet 40 mg (Purdue Pharma) were purchased in Canada.

<sup>§</sup> Expressed as the arithmetic mean (CV%)

<sup>€</sup> Expressed as the arithmetic mean (CV%)

## Study No. R09-0969

A blinded, single-dose, balanced, randomized, two treatment, two period, two sequence, crossover bioequivalence study of RAN-OXYCODONE CR Tablets 40 mg (Ranbaxy Pharmaceuticals Canada Inc.) compared to that of OxyContin® Tablets 40 mg by Purdue Pharma was conducted in 24 healthy, adult, human subjects under fed conditions. A summary of the pharmacokinetic parameters is summarized in the table below:

### SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Oxycodone (1 x 40 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Least Square Means	90% Confidence Interval
AUC <sub>0-t</sub> (ng-hr/mL)	512.17 523.28 (22.68)	529.99 544.06 (25.54)	96.64	(93.70 - 99.67)
AUC <sub>0-inf</sub> (ng-hr/mL)	514.64 525.64 (22.53)	533.58 547.50 (25.31)	96.45	(93.50 - 99.49)
C <sub>max</sub> (ng/mL)	58.02 59.12 (21.59)	52.00 52.78 (20.05)	111.57	(106.00 - 117.44)
T <sub>max</sub> § (h)	4.15 (21.27)	3.08 (40.45)		
T <sub>1/2</sub> € (h)	4.37 (12.15)	5.44 (8.75)		

\* RAN-OXYCODONE CR tablets 40 mg (Ranbaxy Pharmaceuticals Canada Inc.)

† OxyContin® (oxycodone hydrochloride) controlled release tablet 40 mg (Purdue Pharma) were purchased in Canada.

§ Expressed as the arithmetic mean (CV%)

€ Expressed as the arithmetic mean (CV%)

## DETAILED PHARMACOLOGY

### Pharmacodynamics:

Oxycodone and related  $\mu$ -agonist opioids produce their major effects on the CNS and the bowel by acting at specific saturable opioid receptors in the CNS and other tissues. The effects include analgesia, drowsiness, changes in mood, respiratory depression, cough suppression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems.

Oxycodone receptor selectivity has not been extensively studied or characterized, and there appears to be a discrepancy between its weak affinity for opioid receptors and its potent antinociceptive activity.

Oxycodone has been shown to be 2 - 4 times more potent than morphine after both subcutaneous and intraperitoneal administration in rats. In clinical studies in patients with acute post-operative pain, oxycodone has been demonstrated to be twice as potent as morphine.

### TOXICOLOGY

The LD<sub>50</sub> after subcutaneous administration of oxycodone in mice was 275 - 340 mg/kg. The lowest lethal dose has been reported to be 200 mg/kg after subcutaneous administration in mice. These values are similar to those obtained for morphine. In a preliminary 12 day study in rabbits, no drug related toxic effects were discernable at 5 mg/kg. Doses of 25, 75 and 150 mg/kg were associated with variable and transient pharmacotoxic effects typical of high dose opioid treatment in animals (decreased activity, decreased or absent defecation and convulsions).

#### *Teratogenicity:*

Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/day. Also, oxycodone did not induce any malformations in rats at doses as high as 8 mg/kg/day or in rabbits at doses as high as 125 mg/kg/day. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/day group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses  $\geq 2$  mg/kg/day compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/day dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural

and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/day based on body weight effects seen at 6 mg/kg/day). There were no effects on the F2 generation at any dose in the study.

There are no adequate and well-controlled studies in pregnant women, and no studies on fertility or the post-natal effects of intrauterine exposure have been carried out.

*Mutagenicity:*

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5,000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1,500 µg/ml and with activation 48 hours after exposure at doses of up to 5,000 µg/ml, and in the in vivo bone marrow micronucleus test in mice at plasma levels of up to 48 µg/ml. Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1,250 µg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/ml or greater with metabolic activation and at 400 µg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

*Carcinogenicity:*

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

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### PART III: CONSUMER INFORMATION

#### <sup>N</sup>RAN<sup>TM</sup>OXYCODONE CR

Oxycodone Hydrochloride Controlled Release Tablets  
15 mg, 20 mg, 40 mg, 60 mg and 80 mg oxycodone hydrochloride

This leaflet is part III of the "Product Monograph" published when RAN-OXYCODONE CR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RAN-OXYCODONE CR. Contact your doctor or pharmacist if you have any questions about the drug.

**Keep RAN-OXYCODONE CR in a safe place away from children and pets. Accidental use by a child is a medical emergency and may result in death. Never take medicine in front of small children as they will want to copy you. If a child accidentally takes RAN-OXYCODONE CR, get emergency help right away.**

Please read this before you start taking RAN-OXYCODONE CR tablets. Remember this information does not take the place of your doctor's instructions.

#### WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT RAN-OXYCODONE CR?

- Do not cut, break chew, dissolve or crush RAN-OXYCODONE CR tablets before swallowing. If RAN-OXYCODONE CR is taken this way, oxycodone could be released too fast. This can lead to serious and life-threatening breathing problems. Life-threatening breathing problems can also happen because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:
  - o have trouble breathing, or have slow or shallow breathing
  - o have a slow heartbeat
  - o have severe sleepiness
  - o have cold, clammy skin
  - o feel faint, dizzy, confused, or cannot think, walk or talk normally
  - o have a seizure
  - o have hallucinations
- RAN-OXYCODONE CR is not for use to treat pain that you only have once in a while ("as needed")
- Take RAN-OXYCODONE CR exactly as described by your physician. Do not take the 60 mg and 80 mg strength or a single dose of 40 mg or more of RAN-OXYCODONE CR unless you are "opioid tolerant". Your doctor will tell you when you are "opioid tolerant" to a certain dose of RAN-OXYCODONE CR.
- Never give RAN-OXYCODONE CR to anyone else, even if they have the same symptoms as you have. It may harm them or even cause death.
- Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.

- Prevent theft, misuse or abuse. Keep RAN-OXYCODONE CR in a safe place to protect it from being stolen.
- After you stop taking RAN-OXYCODONE CR, you should take the unused tablets to your pharmacist to be destroyed.

#### ABOUT THIS MEDICATION

**RAN-OXYCODONE CR is a controlled substance (opioid class of drugs - Schedule 1) because it contains a narcotic pain killer that can be a target for people who abuse prescription medicines or street drugs.**

Because of their properties that affect the mind and mental processes (psychoactive) and their potential for abuse, opioid pain medications are subject to the Controlled Drugs and Substances Act (CDSA) which provides control of substances that can alter mental processes and that may produce harm to health and to society when diverted or abused.

**With the exception of authorized use, all activities involving controlled substances are prohibited by law in Canada, under the CDSA.**

**What the medication is used for:**

RAN-OXYCODONE CR is an oral controlled release tablet that slowly releases oxycodone (an opioid analgesic) over a 12 hour period, and requires a dose every 12 hours to control your pain.

**What it does:**

Oxycodone is a medicine used to treat moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more.

Oxycodone belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics and also includes codeine, fentanyl, hydromorphone and morphine.

Your pain may increase or decrease occasionally and your doctor may need to change the amount of oxycodone you take daily (daily dosage).

**When it should not be used:**

RAN-OXYCODONE CR should not be used if:

- Your doctor did not prescribe it for you;
- You are allergic to oxycodone, opioids or any other ingredient in the tablets; (see **What the nonmedicinal ingredients are**)
- Your pain is mild;
- Your pain can be controlled by occasional use of any painkillers;
- You have severe asthma or severe lung problems;
- You suffer from alcoholism;
- You have a head injury;
- You suffer from seizures;
- You had surgery less than 12-24 hours ago and you were not taking RAN-OXYCODONE CR just before surgery;

- You have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen;
- You are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medications (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline);
- You are pregnant, in labour or breast-feeding.

Individuals under 18 years of age should not take RAN-OXYCODONE CR tablets.

**What the medicinal ingredient is:**

Oxycodone Hydrochloride

**What the important nonmedicinal ingredients are:**

RAN-OXYCODONE CR Tablets contain: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, povidone. In addition, the tablet coating contains the following: D&C Yellow No.10 Aluminum Lake (for 80 mg tablet), FD&C Blue No.2 (for 15 mg and 80 mg tablet), FD&C Red No.40 ( for 60 mg tablet), FD&C Yellow No.5 (for 40 mg tablet), FD&C Yellow No 6 (for 60 mg tablet), iron oxide ((yellow) for 40 mg tablet), iron oxide ((black, yellow) for 15 mg tablet), iron oxide ((red, yellow) for 20 mg tablet), talc (for 20 mg, 40 mg and 80 mg tablet), titanium dioxide, hypromellose, macrogol.

**What dosage forms it comes in:**

RAN-OXYCODONE CR Tablets; 15 mg, 20 mg, 40 mg, 60 mg and 80 mg.

**WARNINGS AND PRECAUTIONS**

**RAN-OXYCODONE CR tablets are designed to work properly over 12 hours when swallowed whole.**

**If RAN-OXYCODONE CR tablets are abused by crushing, chewing, dissolving, snorting or injecting the product, this leads to quick release and absorption of a higher dose over a short period of time that may cause death.**

**You MUST NOT consume alcoholic beverages, or prescription or nonprescription medications containing alcohol, while on RAN-OXYCODONE CR therapy. This may result in more drug in your bloodstream and may lead to dangerous side effects like what happens when you take more than you prescribed dose. You can die from an overdose of this medication.**

**You must not take other drugs that affect the brain (CNS depressants) together with RAN-OXYCODONE CR, as this may lead to more effects on the brain (CNS depression) that include shallow slow breathing (respiratory depression), low blood pressure (hypotension), feeling very sleepy (profound sedation) or losing consciousness (coma).**

**Keep RAN-OXYCODONE CR out of the reach of children. You should not give RAN-OXYCODONE CR to anyone as**

**inappropriate use may have severe medical consequences, including death.**

BEFORE you use RAN-OXYCODONE CR, talk to your doctor or pharmacist if you have, or had in the past any other medical conditions, especially the following ones: trouble breathing or lung problems, head injury, liver or kidney problems, adrenal gland problems, such as Addison’s disease, convulsions or seizures, alcoholism, hallucinations or other severe mental problems, past or present substance abuse or drug addiction.

Tell your doctor or pharmacist if you are pregnant, plan to become pregnant, or are breastfeeding. RAN-OXYCODONE CR will pass through the milk and may harm the baby. RAN-OXYCODONE CR should not be used in patients who are pregnant or lactating.

If you are planning surgery, or about to undergo surgery, tell your doctor that you are taking RAN-OXYCODONE CR.

You should take the following precautions while taking RAN-OXYCODONE CR tablets:

- You must not consume alcohol while taking RAN-OXYCODONE CR as it may increase the chance of experiencing dangerous side effects;
- Driving or other tasks requiring full alertness should not be attempted until you are sure that taking RAN-OXYCODONE CR does not make you drowsy;
- You must tell your doctor and pharmacist if you are taking any other over-the counter or prescription medications - they will tell you what you should do.

**Abuse, Addiction and Physical Dependence**

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as RAN-OXYCODONE CR. Patients who have taken RAN-OXYCODONE CR for a period of time may develop physical dependence, and should not abruptly stop taking it. See ‘**Discontinuation:**’ section of this leaflet.

While there are important differences between physical dependence and addiction, each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

For more information on the use of this type of medication go to [www.healthcanada.gc.ca/iyh](http://www.healthcanada.gc.ca/iyh). This site provides Health Canada endorsed information on the safe use of opioid medications.

**INTERACTIONS WITH THIS MEDICATION**

- You should not take RAN-OXYCODONE CR if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitor medications (e.g. Phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).

Drugs that may interact with RAN-OXYCODONE CR include:

- **Alcohol or other sedative drugs may enhance the drowsiness caused by oxycodone;**
- **Other opioids, anaesthetics, sedatives, hypnotics, antidepressants, sleeping aids, phenothiazines, neuroleptics, some heart medications (e.g., beta-blockers), chloral hydrate and glutethimide;**
- Antihistamines or sleep aids (these medicines could make you drowsy and depress your breathing);
- Any nonprescription, (over-the-counter) medications;
- Any herbal remedies.

### PROPER USE OF THIS MEDICATION

**RAN-OXYCODONE CR tablets must be swallowed whole and should not be broken, chewed, dissolved or crushed since this can lead to the release and absorption of an excessive dose of oxycodone which can seriously harm you. This is very dangerous. You could die from an overdose of the medicine.**

RAN-OXYCODONE CR is not recommended for rectal administration.

#### Usual dose:

Take the dose prescribed by your doctor. RAN-OXYCODONE CR tablets should be taken every 12 hours with a glass of water.

**Your dose of RAN-OXYCODONE CR will be clearly labelled on the medication bottle. Be sure to follow the directions on the label exactly; this is very important. Do not increase or decrease your dose without consulting your doctor.** If your dosage is changed by your doctor, be sure to write it down at the time your doctor calls or sees you, and follow the new directions exactly. Review your pain regularly with your doctor to determine if you still need RAN-OXYCODONE CR. Be sure to use RAN-OXYCODONE CR only for the condition for which it was prescribed.

You may see tablets in your stools (bowel movements) when using RAN-OXYCODONE CR. Do not be concerned, your body has absorbed the medicine.

**Do not drink alcohol while using RAN-OXYCODONE CR. It may increase the chance of having dangerous side effects including overdose and death.**

#### Discontinuation:

After you stop taking RAN-OXYCODONE CR you should take the unused tablets to your pharmacist to be destroyed.

Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms such as body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, unexplained fever, weakness and yawning.

You should not stop taking RAN-OXYCODONE CR all at once if you have been taking it for more than a few days.

#### Reordering RAN-OXYCODONE CR:

A new written prescription is required from your doctor each time you need more RAN-OXYCODONE CR. Therefore, it is important that you contact your doctor at least three working days before your current supply runs out.

#### Overdose:

The most important sign of overdose is decreased breathing (abnormally slow or weak breathing), dizziness, confusion or extreme drowsiness.

If you accidentally take an overdose of RAN-OXYCODONE CR, call your doctor and/or your local emergency number and/or a Regional Poison Control Centre immediately or go to a hospital emergency and take any remaining tablets and the container with you, even though you may not feel sick.

#### Missed Dose:

It is very important that you do not miss any doses. If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once, unless your doctor tells you to. If you miss several doses in succession, talk to your doctor before restarting your medication.

Do not seek additional prescriptions for this medicine from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase, or any other complaint develop as a result of taking RAN-OXYCODONE CR, tell your doctor immediately.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects you may experience are constipation, nausea, drowsiness, dizziness, vomiting, itching, headache, dry mouth, weakness and sweating. Tell your doctor about these problems if they arise. Your doctor may order a laxative and stool softener to help relieve your constipation while you are taking RAN-OXYCODONE CR.

If you experience any symptoms related to difficulty in breathing, such as tight chest or wheezing, fainting, or rapid heartbeat, seek immediate emergency medical assistance.

#### **RAN-OXYCODONE CR can cause physical dependence.**

Your body will get used to RAN-OXYCODONE CR if you take it more than a few days. You can get sick with withdrawal symptoms if you stop taking RAN-OXYCODONE CR all at once. You can avoid getting sick with withdrawal symptoms by stopping RAN-OXYCODONE CR slowly. Your doctor will tell you how to do this. See withdrawal reactions listed within the Discontinuation section of this leaflet.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety and shivering are also possible after converting from your previous opioid analgesic to RAN-OXYCODONE CR, or converting from RAN-OXYCODONE CR to another opioid. Contact your doctor if you experience these symptoms when switching to or from RAN-OXYCODONE CR.

*This is not a complete list of side effects. For any unexpected effects while taking RAN-OXYCODONE CR, contact your doctor or pharmacist.*

### HOW TO STORE IT

Store between 15° C and 30° C. Keep container tightly closed. Protect from moisture. Keep in cool, dry place.

Keep RAN-OXYCODONE CR in a secure place to prevent theft and misuse.

Do not give RAN-OXYCODONE CR to anyone other than the person for whom it was prescribed, since it may seriously harm them, including death.

Keep RAN-OXYCODONE CR out of the reach of children. Accidental overdose by a child is dangerous and may result in death.

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report on line at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and

-Fax toll-free to 1-866-678-6789 or

-Mail to: Canada Vigilance Program

Health Canada

Postal Locator 0701E

Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the distributor, Ranbaxy Pharmaceuticals Canada Inc., at: 1-866-840-1340.

### RANBAXY

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