PRESCRIBING INFORMATION

ⓃRIVACOCET

(Acetaminophen 325 mg and Oxycodone Hydrochloride 5 mg)

Tablets

Opioid analgesic

Laboratoire Riva Inc.
660, Boul. Industriel
Blainville, Québec,
J7C 3V4

www.labriva.com

Date of revision:
May 3, 2016

Control # **194140**

PRESCRIBING INFORMATION

ⓃRIVACOCET
(oxycodone hydrochloride 5 mg/ acetaminophen 325 mg)

Tablets

THERAPEUTIC CLASSIFICATION

Opioid analgesic

ACTION AND CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in RIVACOCET are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one half of its analgesic activity when administered orally. It has been suggested that less rapid biotransformation in the liver may be due to the protective effect of a methoxy group in the 3-position, the site of glucuronide conjugation in morphine.

RIVACOCET also contains the non-opioid antipyretic analgesic, acetaminophen; the latter exerts its effects by a mechanism similar to that of the salicylates but, unlike the salicylates, does not have anti-inflammatory or uricosuric properties. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract, peak plasma levels being obtained within 10 minutes to 1 hour.

INDICATIONS

For the relief of moderate to moderately severe pain, including conditions accompanied by fever.

CONTRAINDICATIONS

RIVACOCET (oxycodone hydrochloride 5 mg/ acetaminophen 325 mg) tablets should not be administered to patients with:

- Hypersensitivity to oxycodone or acetaminophen or any other component of this product.
- Status asthmaticus, pre-existing respiratory depression or convulsive states.
- Severe hepatic insufficiency or active liver disease.

WARNINGS

Drug Dependence

Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential of being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of RIVACOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral medication containing opioids.

Occupational Hazards

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using RIVACOCET should be cautioned accordingly.

Drug Interactions

Patients receiving other opioid analgesics, general anesthetics, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol), concomitantly with RIVACOCET may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Since the CYP3A4 isoenzyme plays a major role in the metabolism of RIVACOCET, 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 RIVACOCET 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.

Hepatic

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral, and rectal) and all products containing acetaminophen (oral solution/drops, syrup, pills, capsules, suppositories, etc.). Do not exceed the maximum recommended daily dose of acetaminophen (see USE WITH OTHER ACETAMINOPHEN-CONTAINING PRODUCTS).

Administration of acetaminophen doses higher than recommended entails the risk for very serious liver damage. Clinical symptoms of liver damage are usually first seen after one to two days following acetaminophen overdose. Maximum liver damage symptoms are usually observed after 3-4 days (see OVERDOSE). Acetaminophen should be used with caution in cases of hepatic insufficiency and severe renal insufficiency (creatinine clearance ≤30 mL/min).

Hypersensitivity Reactions

Serious skin reactions
Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens – Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at their first appearance

Pregnancy

Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, RIVACOCET should not be given to pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards. The administration of RIVACOCET to obstetrical patients in labor may be associated with respiratory depression of the newborn.

Nursing Women

In view of the potential for opioids to be excreted in breast milk, RIVACOCET should not be used in breast-feeding women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Labour and Delivery

Physical dependence and/or respiratory depression may occur in the infant if opioids are administered during labour.

Pediatrics (< 18 years of age)

RIVACOCET should not be administered to infants or children.

Use with other Acetaminophen-Containing Products

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended daily dose (4000 mg of acetaminophen per day), RIVACOCET should not be used concomitantly with other acetaminophen-containing products.

PRECAUTIONS

Head injury and increased intracranial pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing elevated intracranial pressure. Furthermore, opioids may produce adverse reactions which can obscure the clinical course of patients with head injuries.

Acute abdominal conditions

The administration of RIVACOCET or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients

RIVACOCET should be given with caution to certain patients such as the elderly or debilitated, because of the danger of cardiac or respiratory depression, as well as to those patients with hemorrhage, severe respiratory or renal impairment (creatinine clearance ≤30 mL/min), hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Headache

Because headache often involves a significant psychological component, an opioid analgesic should only be employed for the treatment of headache when no other treatment is effective, in order to minimize the risk of psychological and physical dependence.

Other

Patients should be instructed to store RIVACOCET, as for any medication, safely out of the sight and reach of children.

ADVERSE EFFECTS

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

OVERDOSE

RIVACOCET (oxycodone hydrochloride 5 mg/ acetaminophen 325 mg) is a combination product. The clinical presentation of overdose may include the signs and symptoms of oxycodone toxicity, acetaminophen toxicity or both.

Oxycodone
Serious overdose with acetaminophen and oxycodone tablets is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen
The ingestion of very large amounts of acetaminophen and oxycodone tablets may, in addition, result in acute acetaminophen intoxication, characterized by anorexia, nausea, vomiting and sweating within two or three hours of ingestion, and possibly cyanosis with methemoglobinemia. Within 48 hours, liver function tests rise abnormally, and the liver becomes enlarged and tender. Within three to five days, jaundice, coagulation defects, myocardiopathy, encephalopathy and renal failure occur, followed by death due to hepatic necrosis. The ingestion of 10 g of acetaminophen is considered to result in intoxication, with the possibility of a fatal outcome if the amount exceeds 15 g. Hepatotoxicity occurs when plasma levels of 300 μg/mL are observed within four hours of ingestion.

Treatment of Overdose

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids, including oxycodone. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeat doses of the antagonist should be administered as needed to maintain adequate respiration. The instructions contained in the package insert provided by the manufacturer should be carefully observed.

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 employed as indicated.

Gastric emptying by emesis or lavage may be useful in removing unabsorbed drug, and should be carried out at an early stage of treatment. Plasma levels of acetaminophen should be determined. If hemodialysis is carried out within ten hours of ingestion, it may be of some value.

Overdose treatment includes administration of the antidote, N-acetylcysteine (NAC) by intravenous or oral route, if possible, within 8 hours of ingestion. NAC can give some degree of protection even after 16 hours.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the patient's response. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. The usual RIVACOCET adult dose is one tablet every six hours as needed for pain.

PHARMACEUTICAL INFORMATION

Each white, round, biconvex tablet, engraved “5” and “325” separated by a regular line on one side and plain on the other contains: oxycodone hydrochloride 5 mg and acetaminophen 325 mg.

The oxycodone component is 14-hydroxydihydrocodeinono, a white odorless crystalline power which is derived from the opium alkaloid, thebaine.

Empirical Formula: $C_{18}H_{21}NO_4$

Molecular Weight: 315.36

Acetaminophen (paracetamol, APAP, N-acetyl p-aminobenzoic, 4’-hydroxyacetanilide) is a major active metabolite of phenacetin.

Storage: Store at room temperature (15 to 30°C).

DOSAGE FORM, PACKAGING AND COMPOSITION

RIVACOCET: White, round, biconvex tablet, engraved “5” and “325” separated by a regular line on one side and plain on the other. Available in bottles of 100 and 500.

Composition

Each tablet of RIVACOCET contains: oxycodone hydrochloride 5 mg and acetaminophen 325 mg. Non-medicinal ingredients: Colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch, sodium starch glycolate and stearic acid.

REFERENCE

Prescribing Information PERCOCET® (oxycodone hydrochloride 5 mg / acetaminophen 325 mg), Bristol-Myers Squibb Canada, Revision date: 23 September 2014, Control No: 177089

PART III: CONSUMER INFORMATION

ⓃRIVACOCET
(Acetaminophen and Oxycodone Hydrochloride)
Tablets

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RIVACOCET. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

RIVACOCET is combination product that contains two medications: oxycodone and acetaminophen. Acetaminophen belongs to the group of medications called analgesics (pain relievers) and antipyrectics (fever reducers). Oxycodone belongs to the group of medications called narcotic analgesics. Oxycodone – acetaminophen is used to relieve moderate to moderately severe pain, including conditions associated with fever.

When it should not be used:

You should not use RIVACOCET if:

- Your doctor did not prescribe it for you
- You are allergic to oxycodone, acetaminophen, opioids or to any of the non-medicinal ingredients in the product (see **What the nonmedicinal ingredients are**)
- have a seizure disorder
- have pre-existing respiratory depression have status asthmaticus (unresponsive asthma)
- Your pain is mild
- Your pain can be controlled by occasional use for any painkillers
- You suffer from alcoholism
- You have a head injury
- 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., Nardil®, Parnate®)
- You are taking any other products containing acetaminophen (e.g. TYLENOL®)

What the medicinal ingredients are:

RIVACOCET tablets combine two centrally acting analgesics, oxycodone and acetaminophen.

What the nonmedicinal ingredients are:

Colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch, sodium starch glycolate and stearic acid.

What dosage forms it comes in:

Each RIVACOCET tablet contains oxycodone hydrochloride 5 mg and acetaminophen 325 mg.

WARNINGS AND PRECAUTIONS

Before you begin using RIVACOCET, be sure to inform your doctor or pharmacist of any medical conditions or allergies you may have, any medications you are taking, whether you are pregnant or breast-feeding, and any other significant facts about your health. These factors may affect how you should use this medication and will help your doctor to decide whether you should use RIVACOCET and what extra care should be taken during its use.

DO NOT take with other products containing acetaminophen. Taking more than the maximum daily dose of acetaminophen may cause severe or possibly fatal liver damage.

BEFORE you use RIVACOCET, talk to your doctor or pharmacist if you have, or had in the past any other medical conditions, especially the followings ones:

- Trouble breathing or lung problems
- Head injury
- Kidney problems
- Liver problems. Acetaminophen can cause decreased liver function. People with liver disease or reduced liver function should discuss with their doctor how this medication may affect their medical condition, how their medical condition may affect the dosing and effectiveness of this medication, and whether any special monitoring is needed.
- Adrenal gland problems, such as Addison's disease
- Convulsions or seizures
- Chronic alcoholism
- Hallucinations or other severe mental problems past or present substance abuse or drug addiction

You should take the following precautions while taking RIVACOCET

- You must not consume alcohol while taking RIVACOCET, as it may increase the chance experiencing dangerous side effects;

- Driving or other tasks requiring full alertness should not be attempted until you are sure that taking RIVACOCET does not make you drowsy
- You must tell your doctor and pharmacist if you are taking any other medications, including natural health products, salicylates or other pain and fever relief medications (nonsteroidal anti-inflammatory drugs (NSAIDS), or prescription medications – they will tell you what you should do. (see also section "Interactions With This Medication")
- If you are planning surgery, or about to undergo surgery, tell your doctor that you are taking RIVACOCET.

Pregnancy: This medication should not be used during pregnancy unless the benefits outweigh the risks. If you become pregnant while taking this medication, contact your doctor immediately.

Breast-feeding: This medication passes into breast milk. If you are a breast-feeding mother and are taking oxycodone and acetaminophen, it may affect your baby. Talk to your doctor about whether you should continue breast-feeding.

Children: The safety and effectiveness of using acetaminophen and oxycodone tablets have not been established in children.

Dependence and withdrawal: This medication contains oxycodone. Physical dependence, psychological dependence, and abuse have occurred with the use of oxycodone. People with a history of past or current substance use problems may be at greater risk of developing abuse or addiction while taking this medication. Abuse is not a problem with people who require this medication for pain relief. If this medication is stopped suddenly, you may experience withdrawal symptoms such as anxiety, sweating, trouble sleeping, shaking, pain, nausea, tremors, diarrhea, and hallucinations. If you have been taking this medication for a while, it should be stopped gradually as directed by your doctor.

Serious Skin Reactions (Acute Generalized Exanthematous Pustulosis, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis): Acetaminophen can cause serious skin reactions that can spread to your mouth, lips, face, hands, trunk, arms and legs. This condition is life-threatening.

Liver Injury: Liver injury can occur when more than the maximum daily dose of acetaminophen is taken. Follow your doctor's instructions to know how much acetaminophen you can take in a day. Acetaminophen can be in oral solutions/drops, syrup, pills, capsules, suppositories, intravenous solutions etc. To calculate how much acetaminophen you have had in a day, read the labels on all products to see if they contain acetaminophen. Keep track of how much acetaminophen is in each dose and how much you have taken in a 24 hour period.

INTERACTIONS WITH THIS MEDICATION IT

Tell your doctor or prescriber about all prescription, over-the-counter (non-prescription), and herbal medications you are taking. Also tell them about any supplements you take.

You should not take RIVACOCET if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitor medications (e.g., Nardil®, Parnate®).

You should not take any other medications that contain acetaminophen (including over-the-counter preparations containing acetaminophen), or oxycodone while you are taking RIVACOCET tablets.

Drugs that may interact with RIVACOCET 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) and chloral hydrate
- Some anti-retroviral agents (such as ritonavir and voriconazole).
- 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

The dosage varies according to each individual and can be affected by the severity of the pain as well as each person's response to the medication.

The usual recommended adult dose of RIVACOCET (each tablet contains 5 mg of oxycodone hydrochloride and 325 mg of acetaminophen) is one tablet every 6 hours as needed for pain. RIVACOCET is not recommended for people under 18 years of age.

Many things can affect the dose of a medication that a person needs, such as body weight, other medical conditions, and other medications. **If your doctor has recommended a dose different from the ones listed**

here, do not change the way that you are taking the medication without consulting your doctor.

It is important to take this medication exactly as prescribed by your doctor.

Do not give this medication to anyone else, even if they have the same symptoms as you do. It can be harmful for people to take this medication if their doctor has not prescribed it.

Discontinuation:

This medication may be habit-forming if taken for long periods of time. **Do not stop taking this medication without talking with your doctor.** If this medication is stopped suddenly, you may experience withdrawal symptoms such as anxiety, sweating, trouble sleeping, shakiness, nausea, tremors, diarrhea, or hallucinations. If you plan on stopping the medication, your doctor may want you to reduce the dose gradually to reduce the severity of withdrawal effects.

Overdose:

In case of drug overdose, contact a healthcare practitioner (e.g., doctor) hospital emergency department or regional poison control center, even if there are no symptoms. Within the first 24 hours you may experience increased sweating, nausea, vomiting, stomach pain, and loss of appetite.

Exceeding the recommendations by your doctor can result in respiratory depression (shallow, slow breathing), seizures, liver damage, coma, heart stoppage and death. Taking a significant overdose can result in hepatic toxicity.

Missed Dose:

If you miss a dose, take it as soon as you remember. But, if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most medications have some side effects; however, not all people have the same side effects, and some people experience few, if any, side effects.

When taking RIVACOCET tablets the most common side effects include: nausea, vomiting, constipation, headache, dizziness, lightheadedness or feeling faint, mood changes and sleepiness.

Consult a doctor if:

- You develop allergic reaction such as wheezing, rash or itching;
- You have severe constipation

Stop taking the medication and seek immediate medical attention if *any* of the following occur:

- Convulsions (seizures)
- Signs of a serious allergic reaction (e.g., abdominal cramps, difficulty breathing, nausea and vomiting, or swelling of the face and throat)
- Signs of breathing problems (e.g., shallow, irregular breathing, or slow or troubled breathing)
- Symptoms of overdose (e.g., cold, clammy skin, abnormally slow or weak breathing, severe dizziness, confusion, slow heartbeat, or extreme drowsiness)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Rare	**Serious Skin Reactions (Acute Generalized Exanthematous Pustulosis, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis):** any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain, yellowing of the skin or eyes, dark urine			√
	Liver Injury: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	

This is not a complete list of side effects. Some people may experience side effects other than those listed.
Check with your doctor if you notice any symptom that worries you while you are taking this medication or if you experience serious symptoms.

HOW TO STORE IT

RIVACOCET tablets should be stored at room temperature (15°C to 30°C).

Do not use RIVACOCET tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place away from the sight and reach of children.

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 online at 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 0701D
    Ottawa, Ontario
    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.

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 Prescribing Information, prepared for health professionals, can be found by contacting Laboratoire Riva Inc. at: 1-800-363-7988

This leaflet was prepared by:
Laboratoire Riva Inc.
660 boul. Industriel
Blainville, Québec
Canada, J7C 3V4

www.labriva.com

Last revised: May 3, 2016