PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]APO-OXYCODONE/ACET

Oxycodone and Acetaminophen Tablets, USP
(as Oxycodone Hydrochloride and Acetaminophen)

5 mg / 325 mg

OPIOID ANALGESIC

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets / Oxycodone hydrochloride 5 mg and acetaminophen 325 mg	Microcrystalline cellulose, povidone, starch, sodium starch glycolate, and stearic acid.

INDICATIONS AND CLINICAL USE

Adults
APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) is indicated for the relief of moderate to moderately severe pain, including conditions accompanied by fever.

APO-OXYCODONE/ACET is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age)
The safety and efficacy of oxycodone hydrochloride and acetaminophen has not been studied in the pediatric population. Therefore, the use of APO-OXYCODONE/ACET is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance of APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) 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.
- Patients with severe hepatic insufficiency or active liver disease.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g. bowel obstruction or 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 pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or 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, and during pregnancy, or during labour and delivery (see Serious Warnings and Precautions, and Warnings and Precautions).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen tablets) should only be used in patients for whom alternative treatment options (e.g. non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

APO-OXYCODONE/ACET poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing APO-OXYCODONE/ACET, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). APO-OXYCODONE/ACET should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of APO-OXYCODONE/ACET. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of APO-OXYCODONE/ACET or following a dose increase.

APO-OXYCODONE/ACET must be swallowed whole. Cutting, breaking, crushing,

chewing, or dissolving APO-OXYCODONE/ACET can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental ingestion of even one dose of APO-OXYCODONE/ACET, especially by children, can result in a fatal overdose of APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of APO-OXYCODONE/ACET during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with APO-OXYCODONE/ACET should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of APO-OXYCODONE/ACET and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General
Patients should be instructed not to give APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. APO-OXYCODONE/ACET should be stored securely to avoid theft or misuse.

APO-OXYCODONE/ACET should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking APO-OXYCODONE/ACET as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of APO-OXYCODONE/ACET can occur at particularly high doses. APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) dose reduction or change in opioid may be required.

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.

Abuse and Misuse
Like all opioids, APO-OXYCODONE/ACET is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-OXYCODONE/ACET should be prescribed and handled with caution.

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.

Opioids, such as APO-OXYCODONE/ACET, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

APO-OXYCODONE/ACET is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular
Oxycodone hydrochloride and acetaminophen 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 drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of APO-OXYCODONE/ACET.

The use of APO-OXYCODONE/ACET in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance
As with other opioids, tolerance and physical dependence may develop upon repeated administration of APO-OXYCODONE/ACET and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. 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.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).**

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride and acetaminophen is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to APO-OXYCODONE/ACET; extreme caution and awareness is warranted to mitigate the risk.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects

Oxycodone hydrochloride and acetaminophen and other morphine-like opioids have been shown to decrease bowel motility. Oxycodone hydrochloride and acetaminophen may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Hepatic Effects

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 (400 mg) 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 **DRUG INTERACTIONS**).

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 **OVERDOSAGE**). Acetaminophen should be used with caution in cases of hepatic insufficiency.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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

Use of APO-OXYCODONE/ACET is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic
Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): APO-OXYCODONE/ACET should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when APO-OXYCODONE/ACET is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of

the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

APO-OXYCODONE/ACET should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation**, and **DRUG INTERACTIONS**).

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

Serotonin Syndrome: APO-OXYCODONE/ACET could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. APO-OXYCODONE/ACET should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS).**

Head Injury: The respiratory depressant effects of oxycodone hydrochloride and acetaminophen, 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 hydrochloride and acetaminophen may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, APO-OXYCODONE/ACET must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS).**

Peri-operative Considerations
APO-OXYCODONE/ACET 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 APO-OXYCODONE/ACET for at least 24 hours before the operation and APO-OXYCODONE/ACET should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if APO-OXYCODONE/ACET is to be continued after the patient recovers from the post-operative 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 hydrochloride and acetaminophen 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.

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

Psychomotor Impairment
APO-OXYCODONE/ACET 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 APO-OXYCODONE/ACET with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. APO-OXYCODONE/ACET should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS)**.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of APO-OXYCODONE/ACET, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with APO-OXYCODONE/ACET and following dose increases.

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

To reduce the risk of respiratory depression, proper dosing and titration of APO-OXYCODONE/ACET are essential. Over estimating the APO-OXYCODONE/ACET dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with APO-OXYCODONE/ACET, as in these patients, even usual therapeutic doses of APO-OXYCODONE/ACET may decrease

respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of APO-OXYCODONE/ACET is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Marketing Experience**).

Skin
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.

Special Populations

Special Risk Groups:
APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women:
Studies in human have not been conducted. APO-OXYCODONE/ACET crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-Marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, APO-OXYCODONE/ACET is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opiates, should be readily available if APO-OXYCODONE/ACET is used in this population.

Pediatrics (< 18 years of age):
The safety and efficacy of oxycodone hydrochloride and acetaminophen tablets have not been studied in the pediatric population. Therefore, use of APO-OXYCODONE/ACET is not recommended in patients under 18 years of age.

The more potent formula, APO-OXYCODONE/ACET, should not be administered to infants or children.

Geriatrics (> 65 years of age):
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Patients with Hepatic Impairment:
APO-OXYCODONE/ACET is contraindicated in patients with severe hepatic insufficiency or active liver disease (see **CONTRAINDICATIONS**).

Acetaminophen should be used with caution in cases of hepatic insufficiency.

Patients with Renal Impairment:
Acetaminophen should be used with caution in cases of severe renal insufficiency (creatinine clearance ≤30 mL/min).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of oxycodone hydrochloride and acetaminophen 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 and acetaminophen are 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.

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, tumor 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. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Post-Marketing Experience
Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants:
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and

durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)** and **Psychomotor Impairment**). APO-OXYCODONE/ACET **(**oxycodone hydrochloride and acetaminophen) should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Table 1 – Established or Potential Drug-Drug Interactions

Class (Proper name)	Ref	Oxycodone Effect	Clinical comment
Azole-antifungal agents (e.g. ketoconazole, voriconazole)	CT	↑ C_{max} (1.7 fold) ↑ AUC (3.6 fold)	If co-administration with APO-OXYCODONE/ACET 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.
Macrolide antibiotics (e.g. erythromycin)	T	↓ clearance ↑ plasma concentrations	
Protease inhibitors (e.g. ritonavir)	T	↓ clearance ↑ plasma concentrations	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Use with Other Acetaminophen-Containing Products

Due to the potential for acetaminophen hepatotoxicity at doses higher than the maximum daily dose (4000 mg of acetaminophen per day for adults), APO-OXYCODONE/ACET should not be used concomitantly with other acetaminophen-containing products (see **WARNINGS AND PRECAUTIONS**).

Drug-Laboratory Interactions

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindolacetic acid.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

For acute pain, it is recommended that APO-OXYCODONE/ACET be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. If APO-OXYCODONE/ACET is used for more than 7 days for the management of chronic non-cancer, non-palliative pain, it is recommended that the daily dose not exceed 12 tablets, which is 60 mg oxycodone (90 morphine milligram equivalent). Physicians and

patients should also take into account any other sources of acetaminophen to ensure the maximum 4000 mg daily dose is not exceeded. Each patient should be assessed for their risk prior to prescribing APO-OXYCODONE/ACET as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of APO-OXYCODONE/ACET (see **DOSAGE AND ADMINISTRATION** - Adjustment or reduction of Dosage).

APO-OXYCODONE/ACET should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g. non-opioid analgesics).

APO-OXYCODONE/ACET must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-OXYCODONE/ACET can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment
Adults:
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 adult dose is one tablet every six hours as needed for pain. Provided there is no concomitant use of other products with acetaminophen, the maximum daily dose of APO-OXYCODONE/ACET is 12 tablets, which is 60 mg oxycodone and 3900 mg acetaminophen (see Drug Interactions, Use with Other Acetaminophen-Containing Products).

APO-OXYCODONE/ACET should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

APO-OXYCODONE/ACET is not indicated for rectal administration.

Patients Not Receiving Opioids at the Time of Initiation of Oxycodone Hydrochloride and Acetaminophen Treatment: The usual initial adult dose of APO-OXYCODONE/ACET for patients who have not previously received opioid analgesics is one tablet every six hours as needed for pain.

Patients Currently Receiving Opioids: 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 2** can be used to calculate the approximate daily oral oxycodone dosage that should provide equivalent analgesia. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

Table 2: Opioid Conversion Table			
Opioids	**To convert to oral morphine equivalent**	**To convert from oral morphine multiply by**	**90 MED equivalent dose**
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.
Busse J. The 2017 Canadian guideline for opioids for chronic non-cancer pain. Hamilton (ON): McMaster University; 2017

Patients with Hepatic Impairment:
APO-OXYCODONE/ACET is contraindicated in patients with severe hepatic insufficiency or active liver disease (see **CONTRAINDICATIONS**).

Acetaminophen should be used with caution in cases of hepatic insufficiency (see **WARNINGS AND PRECAUTIONS, Hepatic Effects**).

Patients with Renal Impairment:
APO-OXYCODONE/ACET should be given with caution to patients with renal insufficiency (creatinine clearance ≤30 mL/min) (see **WARNINGS AND PRECAUTIONS***).*

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. APO-OXYCODONE/ACET should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

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 administration of the lowest dose 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.

Adjustment or Reduction of Dosage:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including APO-OXYCODONE/ACET. Withdrawal (abstinence) 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. 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 (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

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 advanced cancer suffering from some of these forms 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.

Disposal
APO-OXYCODONE/ACET should be kept in a safe place, out of the sight and reach of children before, during and after use. APO-OXYCODONE/ACET should not be used in front of children, since they may copy these actions.

APO-OXYCODONE/ACET should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-OXYCODONE/ACET should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Missed Dose
If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

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

Symptoms:
APO-OXYCODONE/ACET (oxycodone hydrochloride and acetaminophen) 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 APO-OXYCODONE/ACET 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 APO-OXYCODONE/ACET 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.

Significant overdoses of acetaminophen may result in potentially fatal hepatotoxicity. The physician should be mindful that there is no early presentation that is pathognomonic for the overdose. A high degree of clinical suspicion must always be maintained.

Due to the wide availability of acetaminophen, it is commonly involved in single and mixed drug overdose situations and the practitioner should have a low threshold for screening for its presence in a patient's serum. Acute toxicity after single dose overdoses of acetaminophen can be anticipated when the overdose exceeds 150 mg/kg. Chronic alcohol abusers, cachectic individuals, and persons taking pharmacologic inducers of the hepatic P450 microsomal enzyme system may be at risk with lower exposures. Chronic intoxication has been reported, rarely, in persons consuming in excess of 150 mg/kg of acetaminophen daily for several days. Hepatotoxicity occurs when plasma levels of 300 mcg are observed within four hours of ingestion.

Treatment:

Oxycodone
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.

Acetaminophen:
Specific Antidote: NAC (N-acetylcysteine) administered by either the intravenous or the oral route is known to be highly effective antidote for acetaminophen poisoning. It is most effective when administered within 8 hours of a significant overdose but reports have indicated benefits to treatment initiated even after 16 hours. It is imperative to administer the antidote as early as possible in the time course of acute intoxication to reap the full benefits of the antidote's protective effects. If hemodialysis is carried out within ten hours of ingestion, it may be of some value.

General Management: When the possibility of acetaminophen overdose exists, treatment should begin immediately and include appropriate decontamination of the GI tract (such as emesis or lavage), proper supportive care, careful assessment of appropriately timed serum acetaminophen estimations evaluated against the Matthew-Rumack nomogram, timely administration of NAC as required and appropriate follow-up care. Physicians unfamiliar with the current management of acetaminophen overdose should consult with a poison control centre immediately. Delays in initiation of appropriate therapy may jeopardize the patient's chances of full recovery.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action
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 are analgesia and sedation.

APO-OXYCODONE/ACET 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.

Pharmacodynamics

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_2 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 hydrochloride and acetaminophen tablets cause 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 poancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:
Oxycodone hydrochloride and acetaminophen tablets may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis 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 manifest 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.

Pharmacokinetics
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.

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract, peak plasma levels being obtained within ten minutes to one hour.

Special Populations and Conditions

Pediatrics: Individuals under 18 years of age should not take APO-OXYCODONE/ACET tablets.

Geriatrics: See **WARNINGS AND PRECAUTIONS**.

Hepatic Impairment: See **WARNINGS AND PRECAUTIONS**.

Renal Impairment: See **WARNINGS AND PRECAUTIONS.**

STORAGE AND STABILITY

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

Patients should be instructed to store APO-OXYCODONE/ACET, as any medication, safely out of the sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-OXYCODONE/ACET, supplied as white, scored tablets in bottles of 100 and 500 tablets. Each white to off-white, scored tablet contains: oxycodone HCl 5 mg and acetaminophen 325 mg. Nonmedicinal ingredients: microcrystalline cellulose, povidone, starch, sodium starch glycolate and stearic acid. The tablet is white to off-white, round, biconvex tablets, engraved “APO” on one side, “5” over score “325” on the other side.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

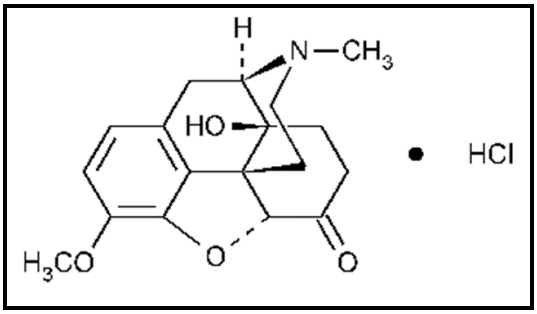
Drug Substance

Proper name: Oxycodone Hydrochloride

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

Molecular formula and molecular mass: $C_{18}H_{21}NO_4$ • HCl and 351.83 g/mol

Structural formula:



Physicochemical Properties:
Oxycodone is a white to off-white powder which is derived from the opium alkaloid, thebaine.

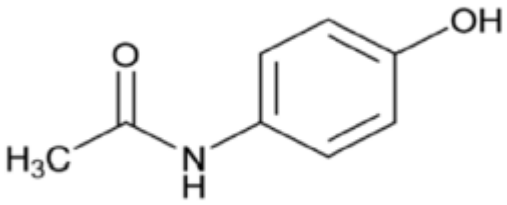
Drug Substance

Proper name: Acetaminophen

Chemical name: Paracetamol, APAP, N-acetyl p-aminobenzoic acid, 4'-hydroxyacetanilide

Molecular formula and molecular mass: $C8H_9NO_2$ and 151.16 g/mol

Structural formula:



CLINICAL TRIALS

A comparative bioavailability study was conducted to determine the relative bioavailability of Oxycodone and Acetaminophen after the administration of APO-OXYCODONE/ACET (Oxycodone HCl/Acetaminophen 5mg/325mg Tablets, Apotex Inc.) and Percocet® (Oxycodone HCl/Acetaminophen 5mg/325 mg Tablets), in 17 healthy male and female volunteers. The study design was blinded, single-dose, two-period, crossover conducted under fasting conditions. Results are summarized in the following tables.

Summary Tables of the Comparative Bioavailability Data

Oxycodone (1 x 5 mg) From measured data **uncorrected for potency** Geometric Mean* Arithmetic Mean (CV %)				
Parameter	Test[€]	Reference[†]	% Ratio of Geometric Means*	90% Confidence Interval*
AUC_T (ng·h/mL)	68.812 70.264 (26.8)	67.268 69.285 (28.2)	102.30	95.02-110.12
AUC_∞ (ng·h/mL)	70.799 72.246 (26.5)	69.643 71.687 (28.3)	101.66	94.50-109.36
C_{max} (ng/mL)	15.212 15.893 (33.6)	13.706 14.171 (30.8)	110.99	97.27-126.65
T_{max}[§] (h)	0.99 (40.1)	0.99 (41.9)		
$T_{½}$[§] (h)	3.84 (19.3)	3.90 (19.0)		

[€]APO-OXYCODONE/ACET Tablets (Oxycodone HCl/Acetaminophen 5mg/ 325mg tablets); Apotex Inc., Toronto, Canada.
[†] Percocet® Tablets (Oxycodone HCl/Acetaminophen 5mg/ 325mg tablets); Bristol-Myers Squibb, Canada.
[§] Expressed as arithmetic mean (CV%) only
*Calculation based on least squares estimate

Acetaminophen (1 x 325 mg) From measured data **uncorrected for potency** Geometric Mean* Arithmetic Mean (CV %)				
Parameter	Test[€]	Reference[†]	% Ratio of Geometric Means*	90% Confidence Interval*
AUC_T (ng·h/mL)	14.620 14.915 (22.2)	14.586 14.839 (20.8)	100.23	95.54-105.15
AUC_∞ (ng·h/mL)	15.743 16.069 (22.4)	15.735 16.039 (21.4)	100.05	95.67-104.62
C_{max} (ng/mL)	4.479 4.774 (35.9)	4.490 4.703 (32.4)	99.74	81.21-122.51
T_{max}[§] (h)	0.94 (106.6)	0.97 (65.7)		
$T_{½}$[§] (h)	3.38 (16.4)	3.25 (19.4)		

[€]APO-OXYCODONE/ACET Tablets (Oxycodone HCl/Acetaminophen 5mg/ 325mg tablets); Apotex Inc., Toronto, Canada.
[†] Percocet® Tablets (Oxycodone HCl/Acetaminophen 5mg/ 325mg tablets); Bristol-Myers Squibb, Canada.
[§] Expressed as arithmetic mean (CV%) only
*Calculation based on least squares estimate

REFERENCE

1. [N]PERCOCET® Product Monograph by Bristol-Myers Squibb Canada, Control #194809, dated October 13, 2016.

2. [N]TEVA-OXYCOCET (Oxycodone hydrochloride 5 mg and Acetaminophen 325 mg) Product Monograph by Teva Canada Limited, Control #216380, dated August 22, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]APO-OXYCODONE/ACET

Oxycodone and Acetaminophen Tablets, USP
(as Oxycodone Hydrochloride and Acetaminophen)
5 mg / 325 mg

Read this carefully before you start taking APO-OXYCODONE/ACET and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about APO-OXYCODONE/ACET.

Serious Warnings and Precautions

- **Even if you take APO-OXYCODONE/ACET as prescribed, you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take APO-OXYCODONE/ACET, it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking APO-OXYCODONE/ACET. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your APO-OXYCODONE/ACET. They could die from taking it. If a person has not been prescribed APO-OXYCODONE/ACET, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took APO-OXYCODONE/ACET while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking APO-OXYCODONE/ACET with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is APO-OXYCODONE/ACET used for?
APO-OXYCODONE/ACET is used to treat pain in adults.

How does APO-OXYCODONE/ACET work?
APO-OXYCODONE/ACET is a combination product that contains two medications: oxycodone hydrochloride and acetaminophen.

Oxycodone is a pain medication belonging to the class of drugs known as opioids which includes codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain. Acetaminophen reduces pain and fever.

What are the ingredients in APO-OXYCODONE/ACET?
Medicinal ingredient: oxycodone hydrochloride and acetaminophen
Non-medicinal ingredients: microcrystalline cellulose, povidone, starch, sodium starch glycolate and stearic acid.

APO-OXYCODONE/ACET comes in the following dosage forms:
Each APO-OXYCODONE/ACET tablet contains 5 mg oxycodone hydrochloride and 325 mg acetaminophen.

Do not use APO-OXYCODONE/ACET if:
- your doctor did not prescribe it for you
- your pain is mild
- you are allergic to oxycodone hydrochloride, acetaminophen or any of the other ingredients in APO-OXYCODONE/ACET (see **What are the ingredients in APO-OXYCODONE/ACET?**)
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have severe liver disease
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a monoamine oxidase inhibitor (MAOI) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-OXYCODONE/ACET. Talk about any health conditions or problems you may have, including if you:
- have a history of illicit or prescription drug or alcohol abuse.
- have severe kidney, liver or lung disease
- are taking other products containing acetaminophen. Acetaminophen can cause decreased liver function. Taking more than the maximum daily dose of acetaminophen may cause severe or possibly fatal liver damage. 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.
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant.

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.

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.

Other warnings you should know about:
Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery:
Do not use APO-OXYCODONE/ACET while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. APO-OXYCODONE/ACET can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to APO-OXYCODONE/ACET. APO-OXYCODONE/ACET can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones.
You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off APO-OXYCODONE/ACET.

Serotonin Syndrome: APO-OXYCODONE/ACET can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take APO-OXYCODONE/ACET with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-OXYCODONE/ACET:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol.
  Do not drink alcohol while you are taking APO-OXYCODONE/ACET. It can lead to:
  - **drowsiness**
  - **unusually slow or weak breathing**
  - **serious side effects or**
  - **a fatal overdose**
- other sedative drugs which may enhance the drowsiness caused by APO-OXYCODONE/ACET
- other opioid analgesics (drugs used to treat pain)
- other medications that contain acetaminophen (including over-the-counter preparations containing acetaminophen), or oxycodone
- general anesthetics (drugs used during surgery)

- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). Do not take APO-OXYCODONE/ACET with MAO inhibitors (MAOI) or if you have taken MAOI's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take APO-OXYCODONE/ACET:
Take **APO-OXYCODONE/ACET** tablets:
- usually every 4 to 6 hours, or as directed by your doctor.
- with a full glass of water

APO-OXYCODONE/ACET tablets:
Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take APO-OXYCODONE/ACET for up to 7 days. If you need to take APO-OXYCODONE/ACET for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need APO-OXYCODONE/ACET. Be sure to use APO-OXYCODONE/ACET only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking APO-OXYCODONE/ACET, tell your doctor immediately.

Stopping Your Medication
If you have been taking APO-OXYCODONE/ACET for more than a few days, you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking APO-OXYCODONE/ACET. You should do it slowly to avoid uncomfortable symptoms such as having:
- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness

- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking APO-OXYCODONE/ACET.

Refilling your Prescription for APO-OXYCODONE/ACET:
A new written prescription is required from your doctor each time you need more APO-OXYCODONE/ACET. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much APO-OXYCODONE/ACET, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:
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. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using APO-OXYCODONE/ACET?
These are not all the possible side effects you may feel when taking APO-OXYCODONE/ACET. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Light headedness
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using APO-OXYCODONE/ACET.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
RARE	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			√
	Respiratory Depression: slow, shallow or weak breathing.			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			√
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
	Low Blood Pressure: dizziness, fainting, light-headedness.	√		
	Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			√
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.		√	
UNKNOWN	**Convulsions (seizures)**			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired APO-OXYCODONE/ACET in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15°C to 30°C).
- **Keep APO-OXYCODONE/ACET out of the sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes APO-OXYCODONE/ACET, get emergency help right away.**

Disposal:

APO-OXYCODONE/ACET should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about APO-OXYCODONE/ACET:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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