

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40257

DRAFT FINAL PRINTED LABELING

OXYCODONE AND ACETAMINOPHEN CAPSULES, USP

5 mg/500 mg



DESCRIPTION

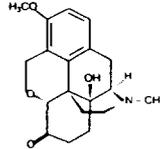
Each Oxycodone and Acetaminophen Capsule, USP 5 mg/500 mg contains:

Oxycodone Hydrochloride, USP..... 5 mg*
Acetaminophen, USP..... 500 mg

*5 mg Oxycodone Hydrochloride, USP is equivalent to 4.4815 mg oxycodone.

In addition, each capsule contains the following inactive ingredients: Gelatin NF, Magnesium Stearate NF, Syloid (Silica Gel NF), Sodium Lauryl Sulfate NF, Pregelatinized Starch NF, Stearic Acid NF, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, and Titanium Dioxide USP.

The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid, thebaine, and may be represented by the structural formula shown below:

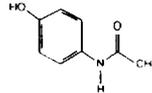


$C_{18}H_{21}NO_4 \cdot HCl$

SPECIMEN

MW = 351.83

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder with a slightly bitter taste. It has the following structural formula:



$C_9H_9NO_2$

MW = 151.17

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic narcotic 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 this product 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.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Oxycodone and Acetaminophen Capsules are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who are hypersensitive to oxycodone or acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, oxycodone and acetaminophen capsules are subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General:

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics 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 increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of products containing oxycodone or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and acetaminophen should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients: 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 taking oxycodone and acetaminophen capsules should be cautioned accordingly.

Drug Interactions: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen may exhibit an additive CNS depression. When such therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with narcotics may produce paralytic ileus.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproductive studies have not been conducted with oxycodone and acetaminophen. It is also not known whether oxycodone and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen should not be given to a pregnant woman unless in the judgement of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of narcotics during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all narcotics, administration of oxycodone and acetaminophen to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers: It is not known whether the components of this product are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

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

Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

Oxycodone and Acetaminophen Capsules are a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused (see WARNINGS).

OVERDOSAGE

Acetaminophen:

Signs and Symptoms: In acute acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Oxycodone:

Signs and Symptoms: Serious overdose with oxycodone 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 overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

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

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and response of the patient. 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 narcotics. Oxycodone and Acetaminophen Capsules USP are given orally.

The usual adult dosage is one capsule every 6 hours as needed for pain.

HOW SUPPLIED

Each OXYCODONE AND ACETAMINOPHEN USP capsule contains Oxycodone Hydrochloride 5 mg (equivalent to 4.4815 mg oxycodone) (see comments under CONTAINER) and Acetaminophen 500 mg. It is available as a Red/Beige hard gelatin capsule imprinted with an MGI 532 identification number.

Bottles of 100 NDC No. 0406-2532-01
Bottles of 500 NDC No. 0406-2532-05

Dispense in a tight, light-resistant container with a child-resistant closure.

Protect from moisture. Store at controlled room temperature 15° to 30°C (59° to 86°F).

DEA Order Form Required.

Rx only

Manufactured by
Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.

Revised 6/98

 MALLINCKRODT

111897B

SPECIMEN

062598



NDC 0406-2532-05

OXYCODONE AND ACETAMINOPHEN CAPSULES, USP



Each capsule contains:
Oxycodone Hydrochloride, USP 5 mg⁺
Acetaminophen, USP 500 mg
Rx only

500 CAPSULES

MALLINCKRODT

USUAL ADULT DOSAGE:
See package insert.

Protect from moisture.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

+5 mg Oxycodone HCl is equivalent to 4.4815 mg oxycodone.

Manufactured by
Mallinckrodt Inc.
St. Louis, Missouri 63134, U.S.A.

AUG 4 1992

NDC 0406-2532-05

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AUG 4 1992

062598



11490

SPECIMEN



NDC 0406-2532-01

OXYCODONE AND ACETAMINOPHEN CAPSULES, USP

Each capsule contains:
Oxycodone Hydrochloride, USP 5 mg*
Acetaminophen, USP 500 mg
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100 CAPSULES

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AUG 4 1998

NDC 0406-2532-01

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