

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40303

DRAFT FINAL PRINTED LABELING

Endo[®]

ENDO GENERIC PRODUCTS

Oxycodone and Acetaminophen Capsules, USP



R_x only



DESCRIPTION

Each capsule, for oral administration, contains:

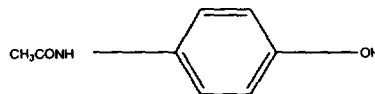
Oxycodone Hydrochloride, USP	5 mg*
Acetaminophen, USP	500 mg

DEC 30

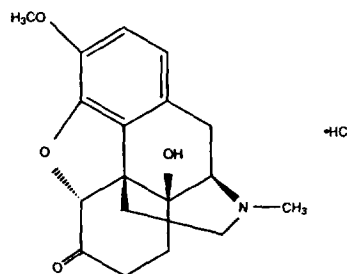
*5 mg oxycodone hydrochloride is equivalent to 4.4815 mg oxycodone.

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized starch and docusate sodium, granular, which contains sodium benzoate. The capsule shell contains gelatin, titanium dioxide, FD&C Red No. 40 and FD&C Yellow No. 6.

Acetaminophen is 4'-hydroxyacetanilide and occurs as a white, odorless crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is C₈H₉NO₂ and the molecular weight is 151.17. It may be represented by the following structural formula:



The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is C₁₈H₂₁NO₄•HCl and the molecular weight is 351.83. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



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 oxycodone and acetaminophen capsules 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

Oxycodone and acetaminophen capsules should not be administered to patients who have previously exhibited hypersensitivity to any component.

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 oxycodone and acetaminophen capsules, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-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 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 increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of oxycodone and acetaminophen capsules or other opioids may obscure the diagnosis or clinical course in 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 using oxycodone and acetaminophen should be cautioned accordingly.

Drug Interactions

Patients receiving other opioid 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 combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with opioids 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 judgment of the physician, the potential benefits outweigh the possible hazards.

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

Labor and Delivery

As with all opioids, 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

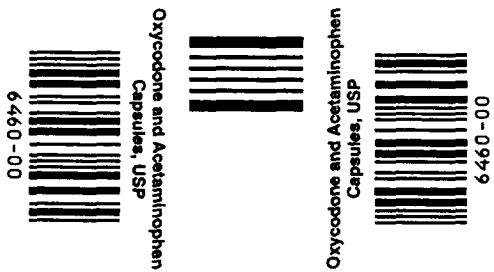
It is not known whether the components of this product are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen capsules are administered to a nursing woman.

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 non-ambulatory 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 overdosage, 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, and within 16 hours of the overdose ingestion for optimal results. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage 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 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 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 the response of the patient. However, it should be kept in mind that tolerance to oxycodone can develop with continued use and that the incidence of untoward effects is dose related. This product is inappropriate even in high doses for severe or intractable pain.

Oxycodone and acetaminophen capsules are given orally. The usual adult dosage is one oxycodone and acetaminophen capsule every 6 hours as needed for pain.

HOW SUPPLIED

Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg reddish orange, hard gelatin capsules, imprinted in white color with "E660" on cap and body are supplied as follows:

Bottles of 100	NDC 60951-660-70
Bottles of 500	NDC 60951-660-85
Unit-Dose Blister Pack of 25 (in Units of 100 Capsules)	NDC 60951-660-75

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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

A Schedule CII Opioid. DEA order form required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317



Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

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Printed in U.S.A.

6460-00/August, 1998

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**Oxycodone and
Acetaminophen
Capsule, USP
5 mg/500 mg**

Manufactured for
Eli Lilly Pharmaceuticals Inc.
Chadds Ford, PA 19317
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Endo ENDO GENERIC PRODUCTS
Oxycodone and Acetaminophen
Capsules, USP

5 mg/500 mg



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5 mg/500 mg



ENDO GENERIC PRODUCTS
Oxycodone and
Acetaminophen
Capsules, USP



Handy

Endo ENDO GENERIC PRODUCTS
Oxycodone and Acetaminophen 5 mg/500 mg
Capsules, USP



DIRECTIONS:

- 1. START WITH UNIT #25 (LOWER RIGHT CORNER) AND WORK SEQUENTIALLY BACKWARDS TO #1.**
- 2. FOR BEDSIDE DISPENSING: TEAR OFF BLISTER ALONG PERFORATIONS.**
- 3. FOR CLINIC DISPENSING: PUSH TABLET OUT BY PRESSING BLISTER.**

