

COMPLETE PRESCRIBING INFORMATION

^NENDOCET*

(oxycodone hydrochloride 5 mg and acetaminophen 325 mg)

Tablets

Opioid Analgesic

Bristol-Myers Squibb Canada
Montreal, Canada

Date of Preparation:
December 31, 1977

Date of Revision:
March 1, 2004

Control No.: 090232

COMPLETE PRESCRIBING INFORMATION

^NENDOCET*

(oxycodone hydrochloride 5 mg and acetaminophen 325 mg)

Tablets

THERAPEUTIC CLASSIFICATION

Opioid Analgesic

ACTION AND CLINICAL PHARMACOLOGY

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

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

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Status asthmaticus, pre-existing respiratory depression or convulsive states, hypersensitivity to oxycodone or acetaminophen.

WARNINGS

Drug dependence

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

Occupational Hazards

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

Interactions with other CNS Depressants

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

Pregnancy

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

Children

The more potent formula, ENDOCET*, should not be administered to infants or children. However, PERCOCET*-DEMI, containing half the amount of oxycodone, can be considered for children of six years of age or older.

PRECAUTIONS

Head injury and increased intracranial pressure

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

Acute abdominal conditions

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

Special risk patients

ENDOCET* should be given with caution to certain patients such as the elderly or debilitated, because of the danger of cardiac or respiratory depression, as well as to those patients with hemorrhage, severe impairment of hepatic, respiratory or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture.

Headache

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

Drug Interactions

The CNS depressant effects of ENDOCET* may be additive with those of other CNS depressants. See WARNINGS.

Other

Patients should be instructed to store ENDOCET*, as any medication, safely out of the reach of children.

ADVERSE REACTIONS

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Serious overdose with ENDOCET* 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. The ingestion of very large amounts of ENDOCET* 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, myocardial pathology, encephalopathy, and renal failure occur, followed by death due to hepatic necrosis. The ingestion of 10 g of acetaminophen is considered to result in intoxication, with the possibility of a fatal outcome if the amount exceeds 15 g. Hepatotoxicity occurs when plasma levels of 300 µg/ml are observed within four hours of ingestion.

Treatment

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 overdose or unusual sensitivity to opioids, including oxycodone. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of

oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeat doses of the antagonist should be administered as needed to maintain adequate respiration. The instructions contained in the package insert provided by the manufacturer should be carefully observed.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

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

The drug PARVOLEX* (N-acetylcysteine, Allen & Hanbury) is a specific antidote for acetaminophen intoxication. For directions for use, refer to the manufacturer's Product Monograph or the CPS.

DOSAGE AND ADMINISTRATION

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

PHARMACEUTICAL INFORMATION

The oxycodone component is 14-hydroxydihydrocodeinone, a white odorless crystalline powder which is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula:

STRUCTURE

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

Molecular Weight: 315.36

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

AVAILABILITY OF DOSAGE FORMS

ENDOCET*, supplied as white, scored tablets in bottles of 100 and 500 tablets.

Each white, scored tablet contains: oxycodone HCl 5 mg and acetaminophen 325 mg. Non-medicinal ingredients: corn starch, microcrystalline cellulose, povidone, pregelatinized starch, silicon dioxide, and stearic acid.

Lactose-, sodium- and tartrazine-free. The tablet is scored on one side and embossed with "0636" on the other.

Storage

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