



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

296 '00 SEP 15 P2:03

King & Spalding
Attention: Jess H. Stribling.
1730 Pennsylvania Ave. N.W.
Washington, D.C. 20006-4706

SEP - 9 2000

Docket No. 00P-1270/CP1

Dear Mr. Stribling:

This is in response to your petition filed on April 25, 2000, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug products: Oxycodone Hydrochloride and Acetaminophen Tablets, 7.5 mg/325 mg and 10 mg/325 mg. The listed drug products to which you refer in your petition are Percocet® (Oxycodone Hydrochloride and Acetaminophen) Tablets, 7.5 mg/500 mg and 10 mg/650 mg manufactured by Endo Pharmaceuticals Inc.

Your request involves a change in strength for the acetaminophen component from that of the listed drug products (i.e., from Oxycodone Hydrochloride and Acetaminophen Tablets 7.5 mg/500 mg to 7.5 mg/325 mg, and from Oxycodone Hydrochloride and Acetaminophen Tablets 10 mg/650 mg to 10 mg/325 mg). The changes you request are the type of changes that are authorized under the Act.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug products.

Under Section 505(j)(2)(C)(i) of the Act, the Agency must approve a petition seeking a strength which differs from the strength of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing strength.

The Agency finds that the change in strength for the specific proposed drug products does not pose questions of safety or effectiveness because the uses, and route of administration of the proposed drug products are the same as that of the listed drug products. The Agency concludes, therefore, that investigations are not necessary in this instance. In addition, if shown to meet bioavailability requirements, the proposed drug product can be expected to have the same therapeutic effect as the listed reference drug product.

When an ANDA is submitted for your proposed drug products, the proposed labeling should reflect the maximum number of tablets per day that can be administered for your proposed drug

00P-1270

PAV/

products. The total daily dose of the acetaminophen component should not exceed the maximum total daily dose for adults of 4000 mg established by the Agency for its safe and effective range. Please refer to the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (53 FR 46204, November 16, 1988).

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the Agency has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug products will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you submit your protocol to the Office of Generic Drugs, Division of Bioequivalence for these drug products prior to the submission of your ANDA. During the review of your application, the Agency may require the submission of additional information,

The listed drug products to which you refer in your ANDA must be the drug products upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,



Gary J. Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20006-470
TELEPHONE 202/737-0500
FACSIMILE: 202/626-3737

DIRECT DIAL:

April 25, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(2)(C)), which authority has been delegated to the Commissioner of Food and Drugs under 21 C.F.R. § 5.10. Petitioner requests the Commissioner of Food and Drugs to declare that abbreviated new drug applications (ANDA) may be submitted for combination oxycodone hydrochloride/acetaminophen tablet products in strengths hereinafter described.

A. Action Requested

King & Spalding requests that the Commissioner declare that ANDAs may be submitted for combination oxycodone hydrochloride/acetaminophen tablet products in strengths of 7.5 mg/325 mg and 10 mg/325 mg.

B. Statement of Grounds

Pain management has received considerable attention in the medical community in recent years. Pain management guidelines published by the Agency for Health Care Policy and Research (AHCPR) acknowledge the common "undertreatment" of pain. See Acute Pain Management Guideline Panel. *Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline*. AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb. 1992; Jacox A, Carr DB, Payne R, et. al. *Management of Cancer Pain. Clinical Practice Guideline No. 9*. AHCPR Pub. No. 94-0592. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services March 1994. As a result of the recommendations contained in these guidelines, physicians have become more aggressive in treating pain.

AHCPR and other current guidelines for the management of both acute and chronic pain recommend extensive reliance on oral opioids in combination with non-opioid analgesics (i.e., NSAIDs and acetaminophen). The objective of such combination therapy is to allow appropriate

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TELEPHONE: 212/558-2100
FACSIMILE: 212/556-2222

1100 LOUISIANA STREET, SUITE 3300
HOUSTON, TX 77002-3219
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FACSIMILE: 713/751-3290

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dosage titration of the opioid (e.g., oxycodone) while administering a safe and effective dose of the non-opioid (e.g., acetaminophen). The dose of the opioid needed is dependent upon the severity of the pain being treated, the degree of tolerance that the patient may have developed, as well as the individual characteristics of the patient such as weight, age, diagnosis, and general medical condition. The daily dose of acetaminophen must not exceed 4000 mg per day to avoid the risk of hepatotoxicity and many doctors prefer to prescribe a lower daily dose of acetaminophen.

The reference listed drug upon which this petition is based is Endo Pharmaceuticals Percocet® (7.5 mg oxycodone hydrochloride/500 mg acetaminophen; 10.0 mg oxycodone hydrochloride/650 mg acetaminophen). The approved labeling for Percocet® states:

Dosage should be adjusted according to the severity of the pain and the 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 opioids. . . . The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams.

The addition of the two proposed formulations containing 7.5 mg oxycodone hydrochloride/325 mg acetaminophen and 10 mg oxycodone hydrochloride/325 mg acetaminophen will respond to the reality of current prescribing practices and make it possible for doctors to individualize the dose of oxycodone while maintaining a safe level of acetaminophen. The maximal daily dose of both proposed products is 12 tablets

AHCPR emphasizes that in using medication to manage pain, the doctor must individualize the regimen to the patient. The addition of these formulations will facilitate the physician's titrating the appropriate dose of oxycodone and acetaminophen against the patient's severity of pain and that patient's response, reserving the formulations containing higher doses of oxycodone for those patients with more severe pain or those who have become tolerant to opioids. Patients will be able to take higher doses of oxycodone without the risk of acetaminophen hepatotoxicity.

Investigations are unnecessary to show the safety and effectiveness of these proposed dosage strengths of 7.5 mg oxycodone hydrochloride/325 mg acetaminophen and 10 mg oxycodone hydrochloride/325 mg acetaminophen. The safety of Percocet® is well established through over twenty years of use. Adverse events associated with Percocet® are well known and are those characteristic of oxycodone and other oral opioids and acetaminophen. The safe maximum daily dose of Percocet® and most other opioid/acetaminophen combinations is

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determined not by the opioid component but rather by the need to limit the dose of acetaminophen to 4000 mg/day.

Oxycodone by itself is currently marketed in approved strengths ranging from 5 mg per tablet to 20 mg/ml solution (e.g., Percolone® 5 mg tablet, M-oxy® 5 mg tablet, Roxicodone® 5 mg tablet and 20 mg/ml oral solution). These products have approved dosage recommendations for adults of 10 mg to 30 mg of oxycodone every four hours as needed with no upper limit on daily dosage being stated.

AHCPR clinical practice guidelines recommend usual starting doses of oxycodone of 10 mg q 3-4 hr for moderate to severe pain, *see id.*, and the American Pain Society's guidelines on Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain recommend a starting dose for oxycodone of 5 mg for mild to moderate pain and 15 to 30 mg for severe pain. American Pain Society, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (4th ed. 1999).

The proposed acetaminophen dose of 325 mg is recognized by FDA as safe and effective both as a single entity and as a constituent of opioid combination analgesics. Acetaminophen purchased over-the-counter is recognized as safe and effective for adults at doses from 325 mg to a maximum single dose of 1000 mg. *See* 53 Fed. Reg. 46204 (1988). With the exception of patients who abuse alcohol or who suffer hepatic dysfunction, daily doses of up to 4000 mg are generally accepted to be safe. *See id.*

The labeling for the proposed formulations is the same as the current approved labeling for the reference listed drug with the variations permitted in 21 C.F.R. 314.94(a)(8)(iv). If a physician prescribes more than 12 tablets per day of the proposed combination of oxycodone hydrochloride 10 mg/acetaminophen 325 mg or the proposed combination of oxycodone hydrochloride 7.5 mg/acetaminophen 325 mg, the total daily dose of acetaminophen would exceed that accepted to be safe. Therefore, the labeling of the proposed products will contain the following safety statement: "The total daily dose of acetaminophen should not exceed four grams."

Draft labeling for the proposed products is included as Exhibit A. To avoid confusion, each product will be named as follows: "[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) [oxycodone hydrochloride/acetaminophen strength]." A side-by-side comparison of the labeling for the reference listed drug and the proposed drug products is included as Exhibit B.

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C. Environmental Impact

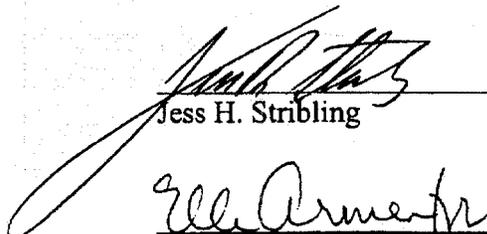
As provided in 21 C.F.R. § 25.3 I, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

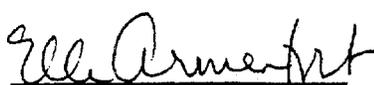
As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Jess H. Stribling



Ellen Armentrout
King & Spalding
1730 Pennsylvania Avenue, NW
Washington, DC 20006
(202) 737-0500

Attachments

A

[TRADENAME]

(Oxycodone and Acetaminophen Tablets, USP) 7.5 mg/325 mg

[TRADENAME]

(Oxycodone and Acetaminophen Tablets, USP) 10 mg/325 mg

CII

R_x only

DESCRIPTION

Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

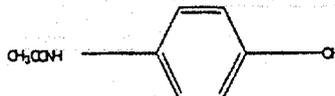
Oxycodone Hydrochloride	7.5 mg*
Acetaminophen, USP	325 mg
Oxycodone Hydrochloride	10 mg*
Acetaminophen, USP	325 mg

* 7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.

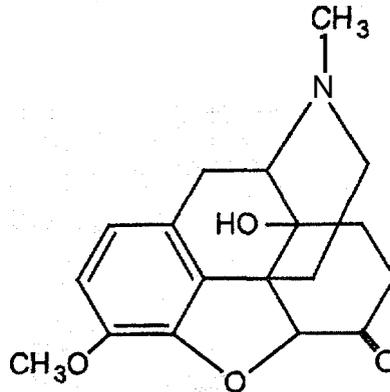
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.

Both strengths of [TRADENAME] also contain the following inactive ingredients:

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17. It may be represented by the following structural formula:



Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic pure opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight 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 involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in [TRADENAME] 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

[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

[TRADENAME] should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other components of this product.

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 [TRADENAME], 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, [TRADENAME] is 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 [TRADENAME] or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: [TRADENAME] 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 [TRADENAME] 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 [TRADENAME] 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.

Usage in Pregnancy

Teratogenic Effects; Pregnancy Category C: Animal reproductive studies have not been conducted with [TRADENAME]. It is also not known whether [TRADENAME] can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

[TRADENAME] 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 [TRADENAME] 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 [TRADENAME] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [TRADENAME] is 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 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

[TRADE NAME] (Oxycodone and Acetaminophen Tablets, USP) is 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. Patient's 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 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 hydrochloride 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. 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. [TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of [TRADENAME] 7.5 mg/325 mg is 12 tablets and the maximal daily dose of [TRADENAME] 10 mg/325 mg is 12 tablets).

HOW SUPPLIED

[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) 7.5 mg/325 mg is supplied as follows:

Bottles of xxx NDC xxxxx-xxx-xx

[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) 10 mg/325 mg is supplied as follows:

Bottles of xxx NDC xxxxx-xxx-xx

Store at 25°C (77°F); excursions permitted to 15°C-30°F (59°-86°F). [See USP Controlled Room Temperature]

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

DEA Order Form Required.

Manufactured for:

Manufactured by:

"Manufacturer"

[TRADENAME] is a Registered Trademark of xxx.

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Printed in U.S.A.

xxxx-xx/April, 2000

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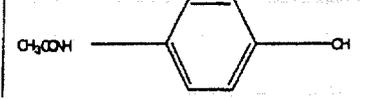
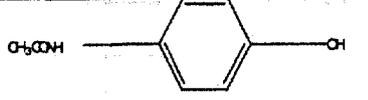
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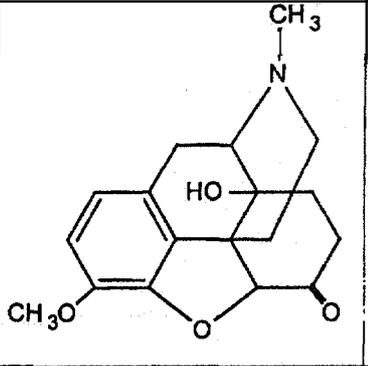
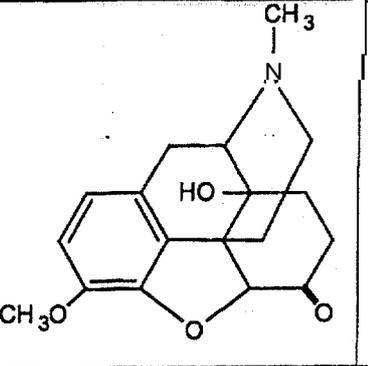
Current Package Insert 6513-00/June, 1999	Proposed Package Insert	Comments
ENDO LABORATORIES		
PERCO CET®		
(Oxycodone and Acetaminophen Tablets, USP)	[TRADE NAME] (Oxycodone and Acetaminophen Tablets, USP) 7.5 mg/325 mg	
	[TRADE NAME] (Oxycodone and Acetaminophen Tablets, USP) 10 mg/325 mg	
CII	CII	
R_x only	R_x only	
DESCRIPTION	DESCRIPTION	
Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:	Each tablet for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:	
Oxycodone Hydrochloride 7.5 mg*	Oxycodone Hydrochloride 7.5 mg*	
Acetaminophen, USP 500 mg	Acetaminophen, USP 325 mg	Change APAP strength,
Oxycodone Hydrochloride 10 mg*	Oxycodone Hydrochloride 10 mg*	
Acetaminophen, USP 650 mg	Acetaminophen, USP 325 mg	Change APAP strength,
• 7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	* 7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.	10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.	
Both strengths of PERCO CET also contain the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. In addition, the	Both strengths of [TRADE NAME] also contain the following inactive ingredients:	Add inactive ingredients.
7.5 mg/500 mg strength contains FD&C Yellow No. 6 Aluminum Lake and the		Colors TBD
10 mg/650 mg strength contains D&C Yellow No. 10 Aluminum Lake.		Colors TBD

<p>Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17. It may be represented by the following structural formula:</p>	<p>Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17. It may be represented by the following structural formula:</p>	
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Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic pure opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight 351.83. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:

Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic pure opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight 351.83. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



CLINICAL PHARMACOLOGY	CLINICAL PHARMACOLOGY	
The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in PERCOCET are analgesia and sedation.	The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in [TRADENAME] 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.	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.	Acetaminophen is a non-opiate, analgesic and antipyretic.	
INDICATIONS AND USAGE	INDICATIONS AND USAGE	
PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is indicated for the relief of moderate to moderately severe pain.	[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) is indicated for the relief of moderate to moderately severe pain.	
CONTRAINDICATIONS	CONTRAINDICATIONS	
PERCOCET should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other components of this product.	[TRADENAME] should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other components of this product.	
WARNINGS	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 PERCOCET, 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, PERCOCET is subject to the	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 [TRADENAME], 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, [TRADENAME] is subject to	

Federal Controlled Substances Act (Schedule II).	the Federal Controlled Substances Act (Schedule II).	
PRECAUTIONS	PRECAUTIONS	
<p>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.</p>	<p>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.</p>	
<p>Acute Abdominal Conditions: The administration of PERCOCET or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.</p>	<p>Acute Abdominal Conditions: The administration of [TRADENAME] or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.</p>	
<p>Special Risk Patients: PERCOCET 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.</p>	<p>Special Risk Patients: TRADENAME 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.</p>	
<p>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 PERCOCET should be cautioned accordingly.</p>	<p>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 [TRADENAME] should be cautioned accordingly.</p>	
<p>Drug Interactions Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS</p>	<p>Drug Interactions Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS</p>	

<p>depressants (including alcohol) concomitantly with PERCOCET may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.</p>	<p>depressants (including alcohol) concomitantly with [TRADENAME] may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.</p>	
<p>The concurrent use of anticholinergics with opioids may produce paralytic ileus.</p>	<p>The concurrent use of anticholinergics with opioids may produce paralytic ileus.</p>	
<p>Usage in Pregnancy Teratogenic Effects; Pregnancy Category C: Animal reproductive studies have not been conducted with PERCOCET. It is also not known whether PERCOCET can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PERCOCET should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.</p>	<p>Usage in Pregnancy Teratogenic Effects; Pregnancy Category C: Animal reproductive studies have not been conducted with [TRADENAME]. It is also not known whether [TRADENAME] can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. [TRADENAME] should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.</p>	
<p>Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.</p>	<p>Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.</p>	
<p>Abor and Delivery: As with all opioids, administration of PERCOCET 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.</p>	<p>Labor and Delivery: As with all opioids, administration of [TRADENAME] 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.</p>	
<p>Nursing Mothers It is not known whether PERCOCET is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PERCOCET is administered to a nursing woman.</p>	<p>Nursing Mothers It is not known whether [TRADENAME] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [TRADENAME] is administered to a nursing woman.</p>	
<p>Pediatric Use Safety and effectiveness in</p>	<p>Pediatric Use Safety and effectiveness in</p>	

pediatric patients have not been established.	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.	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 euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.	Other adverse reactions include 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	DRUG ABUSE AND DEPENDENCE	
PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is a Schedule II controlled substance.	[TRADE NAME] (Oxycodone and Acetaminophen Tablets, USP) is a Schedule II controlled substance.	
Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).	Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).	
OVERDOSAGE	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.	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	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.	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.	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. Patient's 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.	Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patient's 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.	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	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	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.	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 hydrochloride 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.	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 hydrochloride 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.	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.	Gastric emptying may be useful in removing unabsorbed drug.	
DOSAGE AND ADMINISTRATION	DOSAGE AND ADMINISTRATION	
Dosage should be adjusted according to the severity of the pain and the response of the	Dosage should be adjusted according to the severity of the pain and the response of the	

<p>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 opioids. PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of PERCOCET 7.5 mg/500 mg is 8 tablets and the maximal daily dose of PERCOCET 10 mg/650 mg is 6 tablets).</p>	<p>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 opioids. [TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of [TRADENAME] 7.5 mg/325 mg is 12 tablets and the maximal daily dose of [TRADENAME] 10 mg/325 mg is 12 tablets).</p>	
HOW SUPPLIED	HOW SUPPLIED	
PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is supplied as follows:	[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) 7.5 mg/325 mg is supplied as follows:	
<p>7.5 mg/500 mg Peach capsule-shaped tablet embossed with "PERCOCET" on one side and "7.5" on the other.</p> <p>Bottles of 100 NDC 63481-621-70</p>		<p>Color and description of tablet TBD</p>
		<p>Package sizes and NDC TBD</p>
<p>Bottles of 500 NDC 63481-621-85</p>		
<p>Unit dose package of 100 tablets NDC 63481-621-75</p>		
<p>10 mg/650 mg Yellow oval tablet, embossed with "PERCOCET" on one side and "10" on the other.</p> <p>Bottles of 100 NDC 63481-622-70</p> <p>Bottles of 500 NDC 63481-622-85</p>	<p>[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) 10 mg/325 mg is supplied as follows:</p> <p>Bottles of xxx NDC xxxxx-xxx-xx</p>	<p>Color and description of tablet TBD</p> <p>Package sizes and NDC TBD</p>
<p>Unit dose package of 100 tablets NDC 63481-622-75</p>		
<p>Store at controlled room temperature 15°-30°C (59°-86°F).</p>	<p>Store at 25°C (77°F); excursions permitted to 15°C-30°F (59°-86°F). [See USP Controlled Room Temperature.]</p>	<p>Storage condition updated to be compliant with the FDA Modernization Act</p>
<p>Dispense in a tight, light-</p>	<p>Dispense in a tight, light-</p>	

resistant container as defined in the USP, with a child-resistant closure (as required).	resistant container as defined in the USP, with a child-resistant closure (as required).	
DEA Order Form Required.	DEA Order Form Required.	
Manufactured for:	Manufactured for:	
Endo Pharmaceuticals Inc. Chadds Ford, Pennsylvania 19317		
Manufactured by: DuPont Pharma Wilmington, Delaware 19880	Manufactured by: "Manufacturer"	
PERCOCET® is a Registered Trademark of Endo Pharmaceuticals Inc.	[TRADENAME] is a Registered Trademark of xxx.	
Copyright © Endo Pharmaceuticals Inc. 1999	Copyright © 2000 xxx	
Printed in U.S.A.	Printed in U.S.A.	
6513-00/June, 1999	xxxx-xx/April, 2000	Item number and plate code TBD



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

April 25, 2000

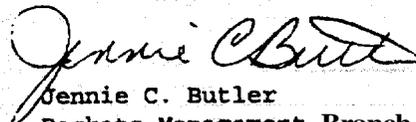
Jess H. Stribling
Ellen Armentrout
King & Spalding
1730 Pennsylvania Ave, NW
Washington, DC 20006

Dear Ms. Stribling:

Your petition requesting the Food and Drug Administration to permit the filing of an ANDA for combination oxycodone hydrochloride/acetaminophen tablet products in strengths of 7.5mg/325 mg and 10 mg/325. was received by this office on 04/25/00. It was assigned docket number 00P-1270/CP 1 and it was filed on 04/25/00. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

sincerely,


Jennie C. Butler
Dockets Management Branch

OCP-1270

ACK 1

KING & SPALDING
191 PEACHTREE STREET
ATLANTA, GEORGIA
30303-1763

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857