

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **40272** _____

Trade Name **Oxycodone and Acetaminophen Tablets USP**
5mg/325mg _____

Generic Name **Oxycodone and Acetaminophen Tablets USP**
5mg/325mg

Sponsor **Duramed Pharmaceuticals, Inc.** _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40272

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology				
Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40272

APPROVAL LETTER

JUN 30 1998

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza, M.S.
5040 Lester Road
Cincinnati, OH 45213



Dear Sir:

This is in reference to your abbreviated new drug application dated August 26, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

Reference is also made to your amendments dated April 21, 1998, June 26 and June 29, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Percocet Tablets, 5 mg/325 mg of Endo Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/


Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

per 6-30-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40272

FINAL PRINTED LABELING

**Oxycodone and
Acetaminophen
Tablets, USP**



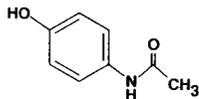
1003360498

DESCRIPTION

Each tablet of oxycodone and acetaminophen contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen, USP 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

Oxycodone and acetaminophen tablets, USP, for oral administration, also contain the following inactive ingredients: croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid.

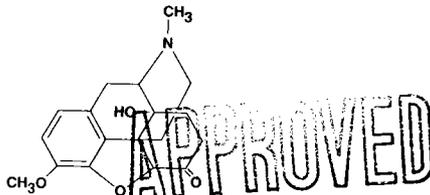
Acetaminophen occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The structural formula is:



C₉H₉NO₂

M.W.: 151.17

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 following structural formula:



C₁₈H₂₁NO₄

M.W.: 315.37

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic narcotic 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 this drug 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 tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Oxycodone and acetaminophen tablets 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 oxycodone and acetaminophen tablets, and they 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 tablets 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 oxycodone and acetaminophen tablets or other narcotics 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 tablets 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 combined 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 tablets. 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 narcotics during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all narcotics, administration of oxycodone and acetaminophen tablets 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 drug are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients has 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

Oxycodone and acetaminophen tablets 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. 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 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 overdose, 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 overdose 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. 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 narcotics.

Oxycodone and acetaminophen tablets, USP are given orally. The usual adult dosage is one tablet every 6 hours as needed for pain.

JUN 30 1998

HOW SUPPLIED

Oxycodone and acetaminophen tablets, USP (5 mg oxycodone hydrochloride and 325 mg acetaminophen tablets, USP), supplied as a round, white to off-white, flat, beveled edge tablet, bisected on one side and debossed "610" on the other side.

Bottles of 100	NDC 51285-610-02
Bottles of 500	NDC 51285-610-04
Bottles of 1000	NDC 51285-610-05

Store at controlled room temperature 15°-30°C (59°-86°F).
DEA Order Form Required.

Rx only

Duramed Pharmaceuticals, Inc.
Cincinnati, Ohio 45213 USA

100336

Iss. 04/98



00336


OXYCODONE AND
ACETAMINOPHEN
TABLETS, USP



NDC 51285-610-05

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

1000 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00648 ISS. 4/98



NDC 51285-610-05

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

1000 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00648 ISS. 4/98



NDC 51285-610-05

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

1000 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00648 ISS. 4/98





NDC 51285-610-04

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

500 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00627 188. 4/98



0 28176 61004 5



NDC 51285-610-04

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

500 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00627 188. 4/98



0 28176 61004 5



NDC 51285-610-04

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only

500 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:

Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00627 188. 4/98



0 28176 61004 5

9

Margo



NDC 51285-610-02

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only
100 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a light, light-resistant container as defined in the USP with child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:
Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

Lot: 498

L00028



0 28176 61002 1



NDC 51285-610-02

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only
100 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a light, light-resistant container as defined in the USP with child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:
Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

Lot: 498

L00028



0 28176 61002 1



NDC 51285-610-02

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only
100 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a light, light-resistant container as defined in the USP with child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:
Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

Lot: 498

L00028



0 28176 61002 1



NDC 51285-610-02

Oxycodone and Acetaminophen Tablets, USP

5mg*/325mg

Each tablet contains:
Oxycodone hydrochloride 5 mg*
Acetaminophen 325 mg

Rx only
100 Tablets

USUAL ADULT DOSAGE: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in a light, light-resistant container as defined in the USP with child resistant closure.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Lot No.:
Exp. Date:

*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

Lot: 498

L00028



0 28176 61002 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40272

CHEMISTRY REVIEW(S)

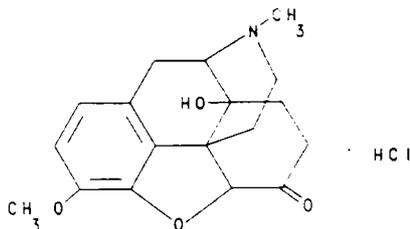


Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch V
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2
2. ANDA # 40-272
3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213
4. LEGAL BASIS FOR SUBMISSION
The legal basis is the reference listed drug Percocet held by DuPont Pharma. The drug product is not entitled to a period of marketing exclusivity described under 505 (j) (4) (d).
5. SUPPLEMENT (s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone and Acetaminophen
Tablets
8. SUPPLEMENT (s) PROVIDE (s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

Orig. Submission	8/26/97
Ack Ltr	9/26/97
Amendment	4/21/98
Amendment	6/25/98
10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF (s)
13. DOSAGE FORM
Tablets
14. POTENCY
5 mg/325 mg
15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (oxycodone) N-4-hydroxyphenyl acetamide (acetaminophen)

Oxycodone
Hydrochloride



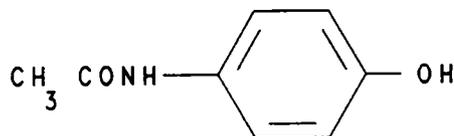
Molecular Formula: $C_{18}H_{21}NO_4 \cdot HCl$

Molecular Weight: 351.83

1. Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5 α)-;
2. 4,5 α -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride.
3. 14-Hydroxydihydrocodeinone (Oxycodone component).

A white, odorless crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine. Long rods from water, dec 270° - 272°C. $[\alpha]_D^{20}$ -125° (c = 2.5). One gram dissolves in 10 mL water. Slightly soluble in alc.

Acetaminophen



Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

1. Acetamide, N-(4-hydroxyphenyl)-;
2. 4'-Hydroxyacetanilide.

A white, odorless crystalline powder, possessing a slightly bitter taste. Large monoclinic prisms from water, mp 169 - 170.5°C. d_4^{25} 1.293. uv max (ethanol): 250 nm (e 13,800). Very slightly sol in cold water, considerably more sol in hot water. Sol in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate. Slightly sol in ether. Practically insol in petr ether, pentane, benzene. LD₅₀ in mice (mg/kg): 338 orally, 500 i.p.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
A. Langowski

DATE COMPLETED:
5/20/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40272

BIOEQUIVALENCE REVIEW(S)

Oxycodone HCl/Acetaminophen
5 mg/325 mg Tablets
ANDA #40-272
Reviewer: Moheb H. Makary
WP #40272D.897

Duramed Pharmaceuticals, Inc.
Cincinnati, OH
Submission Date:
August 26, 1997

Review of a Dissolution Data and Waiver Request

I. Objective:

The firm has requested a waiver of the in vivo bioequivalence requirements for its Oxycodone HCl 5 mg and Acetaminophen 325 mg Tablets USP. The firm conducted dissolution testing on its test product comparing it to Dupont Merck's Percocet^R 325 mg/5 mg Tablet.

Oxycodone HCl/ Acetaminophen Tablets are coded AA for various strengths in the Orange Book.

II. Dissolution Testing:

The following USP 23 conditions were used:

Apparatus: 2 (paddle) at 50 rpm
Medium: 900 mL of 0.1N HCl
Test product: Duramed's Oxycodone HCl/Acetaminophen 5 mg/325 mg Tablets, lot #970301S and lot #970302S
Reference product: Dupont's Percocet^R (Acetaminophen/Oxycodone 325 mg/5 mg) Tablets, lot #EKJ353A
Specifications: NLT 75%(Q) of the labeled amounts of Oxycodone and Acetaminophen are dissolved in 45 minutes.

The dissolution testing results are shown in Table I and II.

III. Formulation:

The formulation of the test product is shown in Table III.

IV. Comment:

The dissolution testing results for the test product met the USP specifications.

V. Recommendations:

1. The dissolution testing conducted by Duramed Pharmaceuticals Inc., on its Oxycodone HCl/Acetaminophen, 5 mg/325 mg Tablets, lots #970301S and lot #970302S, is acceptable. The waiver of the in vivo bioequivalence study requirements is granted for the test product Oxycodone HCl/Acetaminophen, 5 mg/325 mg Tablets based on 21 CFR 320.22 (c). The Division of Bioequivalence deems Oxycodone HCl/Acetaminophen, 5 mg/325 mg Tablets, manufactured by Duramed Pharmaceuticals Inc., to be bioequivalent to Percocet^R 325 mg/5 mg Tablets, manufactured by Dupont Merck.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl, at 37 °C using USP 23 apparatus 2 (paddle) at 50 rpm.

The test product should meet the following specifications:

Not less than 75% of the labeled amount of both acetaminophen and oxycodone in the dosage form are dissolved in 45 minutes.

The firm should be informed of the above recommendations.

/s/ [Redacted]

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /s/ [Redacted]
FT INITIALLED RMHATRE [Redacted]

12/22/97

Concur: /s/ [Redacted]

Date: 12/31/97

Dale Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/11-19-97, 12-17-97 wp 40272W.897

cc: ANDA #40-272, (original), HFD-658 (Makary), Drug File.

TABLE I
COMPARATIVE DISSOLUTION PROFILES FOR OXYCODONE AND ACETAMINOPHEN TABLETS, USP, 5 mg AND 325 mg
FROM DURAMED AND DUPONT

RUN TIME (mins)	Active Component	DURAMED PHARMACEUTICALS OXYCODONE AND ACETAMINOPHEN TABLETS, USP 5 mg AND 325 mg LOT # 970301S % ACTIVE DISSOLVED						DUPONT PHARMA PERCOCET® TABLETS 5 mg AND 325 mg LOT # EKJ353A % ACTIVE DISSOLVED									
		1	2	3	4	5	6	Mean of 12	Max. of 12	1	2	3	4	5	6	Mean of 12	Max. of 12
15	Oxycodone HCl	7	8	9	10	11	12	% RSD of 12	Min. of 12	7	8	9	10	11	12	% RSD of 12	Min. of 12
		(b)(4)(CC)						93.8	(b)(4)(CC)	(b)(4)(CC)						90.3	(b)(4)(CC)
30	Acetaminophen	(b)(4)(CC)						6.9		(b)(4)(CC)						3.7	
		(b)(4)(CC)						93.8		(b)(4)(CC)						64.4	
45	Oxycodone HCl	(b)(4)(CC)						2.0		(b)(4)(CC)						3.4	
		(b)(4)(CC)						96.6		(b)(4)(CC)						96.6	
45	Acetaminophen	(b)(4)(CC)						5.1		(b)(4)(CC)						3.6	
		(b)(4)(CC)						94.6		(b)(4)(CC)						77.8	
45	Oxycodone HCl	(b)(4)(CC)						1.6		(b)(4)(CC)						4.6	
		(b)(4)(CC)						96.9		(b)(4)(CC)						97.7	
45	Acetaminophen	(b)(4)(CC)						4.0		(b)(4)(CC)						3.4	
		(b)(4)(CC)						94.3		(b)(4)(CC)						82.8	
		(b)(4)(CC)						2.1		(b)(4)(CC)						4.7	

Note: USP specifications: NLT 75% (Q) in 45 minutes for both, Oxycodone Hydrochloride and Acetaminophen .
Apparatus: USP Apparatus 2 (Paddle); Medium: 0.1N HCl; Rotation: 50 RPM; Volume: 900 mL

T II
COMPARATIVE DISSOLUTION PROFILES FOR OXYCODONE AND ACETAMINOPHEN TABLETS, USP, 5 mg AND 325 mg
FROM DURAMED AND DUPONT

RUN TIME (mins)	Active Component	DURAMED PHARMACEUTICALS OXYCODONE AND ACETAMINOPHEN TABLETS, USP 5 mg AND 325 mg LOT # 970302S % ACTIVE DISSOLVED						DUPONT PHARMA PERCOCET® TABLETS 5 mg AND 325 mg LOT # EKJ353A % ACTIVE DISSOLVED					
		1	2	3	4	5	6	1	2	3	4	5	6
15	Oxycodone HCl	Mean of 12						Mean of 12					
		Max. of 12						Max. of 12					
	Acetaminophen	% RSD of 12						% RSD of 12					
		Min. of 12						Min. of 12					
30	Oxycodone HCl												
	Acetaminophen												
45	Oxycodone HCl												
	Acetaminophen												
		92.8						90.3					
		2.9						3.7					
		93.8						64.4					
		1.9						3.4					
		95.0						96.6					
		2.5						3.6					
		96.4						77.8					
		1.9						4.6					
		94.6						97.7					
		1.7						3.4					
		96.9						82.8					
		1.4						4.7					

Note: USP specifications: NLT 75% (Q) in 45 minutes for both, Oxycodone Hydrochloride and Acetaminophen .
 Apparatus: USP Apparatus 2 (Paddle); Medium: 0.1N HCl; Rotation: 50 RPM; Volume: 900 mL

Table III

Oxycodone and Acetaminophen Tablets, USP, 5 mg and 325 mg

Ingredient	Qty per Tablet (mg)	(b)(4)(CC)
Tablet Composition		
Acetaminophen (b)(4)(TS)		
Oxycodone Hydrochloride, USP	5.00	(b)(4)(TS)
Microcrystalline Cellulose, NF (b)(4)(CC)	(b)(4)(TS)	
Pregelatinized Starch, NF (b)(4)(TS)		
Croscarmellose Sodium, NF		
Magnesium Stearate, NF		
Total	520.00	(b)(4)(TS)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40272

ADMINISTRATIVE DOCUMENTS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 40-272

APPLICANT: Dūramed Pharmaceuticals, Inc.

DRUG PRODUCT: Oxycodone Hcl/Acetaminophen Tablets, 5 mg/325 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/



Dale Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #40-272
ANDA DUPLICATE
DIVISION FILE
HFD-600/Division Sign Off
HFD-658/Reviewer Moheb H.Makary
BIO DRUG FILE
FIELD COPY

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BIOEQUIVALENCY - ACCEPTABLE Submission Date: August 26, 97

7. **DISSOLUTION WAIVER (DIW)**

Strengths: 5/325 mg
Outcome: AC

DIVISION REVIEW SUMMARY

ANDA: 40-272

FIRM: Duramed Pharmaceuticals

DOSAGE FORM: Tablet STRENGTH: 5 mg/325 mg

DRUG: Oxycodone and Acetaminophen

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable as of 12/01/97..

BIO STUDY INFORMATION: Waiver granted 12/22/97.

METHODS VALIDATION: The drug substance and drug product are articles of the USP. Methods verification was performed and found acceptable 12/31/97.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in the market container.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	SPECIFICATION	METHOD
Description	Round, white to off-white, flat, beveled edge tablet bisected on one side and debossed "dp610" on the other.	In-house
(b)(4)(CC)		In-house
		In-house

Dissolution	(S1) 6 tablets. No individual tablet is less than 80% in 45 min. Q=75%. (S2) Avg of 12 must be equal to or greater than 75% and none less than 60%. (S3) Avg of 24 tabs must be equal to or greater than 75% and not more than 2 tablets are less than 60% and none is less than 50%	USP
Assay	90.0-110.0%	USP
(b)(4)(CC)		In-house
		In-house

LABELING: Satisfactory. See review dated 6/2/98.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

The firm manufactured two exhibit batches in order to qualify two bulk drug manufacturers. The batch sizes were (b)(4)(CC) tablets for each batch. A copy of the executed batch record for lot #970301S begins on p. 208. The (b)(4)(CC) results are within limits. The (b)(4)(CC). The bulk tablet (b)(4)(CC)

A copy of the executed batch record for lot #970302S begins on p. 313. The manufacturing instructions are equivalent to those specified in the blank batch record. The (b)(4)(CC) results are within limits. The (b)(4)(CC)
(b)(4)(CC)

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The applicant states that the process and equipment to be used for the intended production batches are the same, except that a

larger capacity (b)(4)(CC) [redacted] will be used. The intended production batch size is (b)(4)(CC) [redacted] tablets.

RECOMMENDATION: Approvable.

SIGNATURE: /S/ [redacted]
VV V

DATE: 6/15/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40272

CORRESPONDENCE



The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

Patricia
5/19/98

April 21, 1998

Mr. Frank O. Holcomb, Jr., Ph.D.
Director, Division of Chemistry II
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FP
AM

RE: ANDA 40-272 for Oxycodone and Acetaminophen Tablets, USP, 5 mg/325 mg
Subject: Response to Minor Deficiency Letter

Dear Mr. Holcomb:

Reference is made to your letter, dated April 3, 1998, concerning the chemistry review of ANDA 40-272 for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg. In that letter you describe five deficiencies, all of which are now responded to in this minor amendment; however, comment four concerning a request for submission of an impurity validation report has been previously answered.

The issue of impurities and validation of a method for such was raised by the FDA Newark (Parsippany Resident Post) District Office as part of their October 1997 pre-approval inspection for this ANDA at our Somerset, New Jersey manufacturing facility. This FDA inspection resulted in additional analytical work being completed and an impurity validation report being submitted to the District in November 1997. In addition, impurity specifications were established for the drug product and are included in this response.

In a conversation with Mr. Andrew Langowski, Reviewing Chemist in your Division on April 9, 1998, I informed him that the comments in the chemistry deficiency letter were minor except for comment number four concerning impurity method validation. I also informed him that an impurity validation report had been completed and submitted to the Newark District as part of our response to an FDA 483 resulting from a pre-approval inspection of the Somerset, NJ manufacturing site for this drug product.

The Newark District has reviewed the impurity validation report, as well as the rest of our FDA 483 response, and concluded its review with a recommendation of approval. We have included a copy of the District's letter documenting this recommendation.

RECEIVED

APR 22 1998

GENERIC DRUGS

Handwritten signature

Page 2 of 2

To: Mr. Frank O. Holcomb, Jr., Ph.D.

Subject: ANDA 40-272 for Oxycodone and Acetaminophen Tablets, USP, 5 mg / 325 mg

While the reference FDA deficiency letter is classified as a major deficiency, we believe, given the previous response to the impurity question, that this deficiency letter should be re-classified as a minor amendment. The other four chemistry questions in the deficiency letter are minor, requesting only clarification and an update on stability results to include impurity data.

In addition to responding to these minor chemistry deficiencies, we have also included our response to comments from the Labeling Review Branch. Our labels and labeling are now submitted in final printed format.

This minor amendment consists of two (2) copies, an archival copy and a review copy.

We certify that a true copy of this amendment has been provided to the FDA, Resident Post, Parsippany, New Jersey.

If you have any questions or require any additional information, please contact Dr. Nanik D. Gyan, Associate Director, Regulatory Affairs, Somerset, NJ at (732) 563-2245, or the undersigned by telephone at (513) 458-7274, or by fax at (513)731-6482.

Sincerely,



John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

enclosures:

Form FDA 356h

cc: Dr. N. Gyan



The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900
(800) 545-8338

505(j) 11(2)
OK [Signature] 9/22/97
[Redacted]

August 26, 1997

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA for Oxycodone HCl and Acetaminophen Tablets, USP, 5 mg and 325 mg

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today an original abbreviated new drug application (ANDA) seeking approval to market Oxycodone Hydrochloride and Acetaminophen Tablets, USP, 5 mg and 325 mg, that is equivalent to the reference drug, Percocet® Tablets, manufactured by DuPont Merck pursuant to NDA # 85-106.

Duramed's Oxycodone Hydrochloride and Acetaminophen Tablets, USP

- (1) Is a pre-1962 DESI drug product;
- (2) Contains the active drug ingredients in the same concentration and dosage form as Percocet® Tablets; and
- (3) The tablets are listed with an "AA" code in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

The drug product meets the requirements of 21 CFR, 320.22(c); thus, the Bioavailability/Bioequivalence section contains a request for waiver of the requirement for submission of evidence of in vivo bioequivalence.

Oxycodone Hydrochloride and Acetaminophen Tablets, USP, 5 mg and 325 mg are stable and a two year expiration dating is requested for all package sizes. The two year expiration dating is supported by accelerated stability testing.

This ANDA consists of two (2) volumes. The archival copy (blue folders) of this application contains all the information required in the ANDA. The technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. A separate copy of the Bioequivalence section is provided in an

RECEIVED

AUG 27 1997

GENERIC DRUGS

Page 2 of 2

To: Mr. Douglas L. Sporn

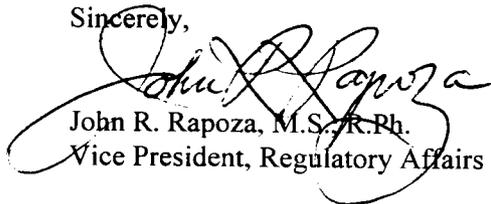
Subject: ANDA for Oxycodone HCl and Acetaminophen Tablets, USP, 5 mg and 325 mg

For detailed information on the organization of this application, please refer to the following "EXECUTIVE SUMMARY - Organization of the ANDA".

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Food and Drug Administration, North Brunswick Resident Post, North Brunswick, New Jersey.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, or the undersigned at (513) 458-7274, or (513-731-6482 FAX).

Sincerely,



John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

enclosures:

Form FDA 356h

Executive Summary - Organization of the ANDA

Duramed's Oxycodone Hydrochloride and Acetaminophen Tablets, USP, 5 mg and 325 mg, ANDA is organized in the manner recommended by the Office of Generic Drugs in its Policy and Procedure Guide 30-91, as modified by the October 14, 1994 letter to industry issued by FDA.

This ANDA is divided into 20 sections, each of which is designated by a roman numeral. A Table of Contents is provided that cross-references each section, as well as significant subparts of the individual sections, to the actual page number where the section or subpart begins. Tabbed divider sheets are provided for each section and subsection and bear the identity of the section to which the tab relates (e.g., "Section V - Labeling").

For ease of reference, the entire ANDA is numbered sequentially in the lower center of each page so that both text and attachments bear consecutive numbering. Page numbers commence on the form 356h.

Whenever a section or subsection references either text or an attachment, a cross-reference will be provided to the location where the referenced text or attachment can be found in the ANDA. If an attachment is referenced more than once, it will only be physically included once in the submission.

Duramed is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA. The second copy of the ANDA consists of a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section which is provided in separate orange folders.

ANDA 40-272

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213



Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Oxycodone and Acetaminophen Tablets USP,
5mg/325mg

DATE OF APPLICATION: August 26, 1997

DATE OF RECEIPT: August 27, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

/s/


Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-272
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/PRickman, Chief/S/ [REDACTED] date 9/26/97
HFD-615, GDavis, CSO [REDACTED] date
HFD-647, SBasaran, Sup. Chem. [REDACTED] date
WP File x:\new\firmam\duramed\ltrs&rev\40272.ack
FT/njg/9/22/97
ANDA Acknowledgment Letter!