

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

76-168

Generic Name: Oxycodone Hydrochloride Extended-
release Tablets, 80mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: March 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-168

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	X
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

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APPLICATION NUMBER:

76-168

APPROVAL LETTER

ANDA 76-168

MAR 23 2004

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Rd.
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 8, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxycodone Hydrochloride Extended-release Tablets, 80 mg.

Reference is also made to the tentative approval letter issued by this office on September 29, 2003, and to your amendments dated December 19, 2003, and January 14, and February 5, 2004. We also acknowledge your correspondence dated January 29, February 18, February 25, and March 4, 2004, addressing TEVA's Risk Management Plan (RMP) for this drug product.

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 Hydrochloride Extended-release Tablets, 80 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Oxycontin[®] Extended-release Tablets, 80mg, of Purdue Pharma LP.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme) at 37°C using USP Apparatus I (basket) at 100 rpm. The test product should meet the following "interim" specifications:

<u>Time</u>	<u>Percent Dissolved</u>
1 hour	_____
4 hours	_____
12 hours	NLT _____

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if there are no revisions to be made to the "interim" specifications or if the final specifications are tighter than the "interim" specifications. In all other instances, the data should be submitted in the form of a Prior Approval Supplement.

The reference listed drug product in your application, Oxycontin® Extended-release Tablets, 80 mg, of Purdue Pharma LP, is subject to multiple periods of patent protection. The following United States patents and their expiration dates currently appear in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

<u>Patent Number</u>	<u>Expiration Date</u>
4,861,598	August 29, 2006
4,970,075	August 29, 2006
5,266,331	October 26, 2007
5,549,912	October 26, 2007
5,656,295	October 26, 2007
5,508,042	April 16, 2013

Your application contains patent certifications to each of these patents under Section 505 (j) (2) (A) (vii) (IV) of the Act stating that none of the claims of the 4,861,598, 5,266,331, 5,549,912, 5,508,042, 5,656,295 and 4,970,075 patents will be infringed by your commercial manufacture, use, or sale of Oxycodone Hydrochloride Extended-release Tablets 80 mg under this ANDA. Section 505(j) (5) (B) (iii) of the Act provides that approval shall be made effective immediately unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This infringement action must be brought before the expiration of forty-five days from the date the notice(s) TEVA provided under paragraph (2) (B) (i) were received by the NDA and patent holders. You have notified the Agency that TEVA has complied with the requirements of Section

505(j)(2)(B) of the Act. As a result, litigation was filed against TEVA in the United States District Court for the Southern District of New York involving a challenge to the '042 patent, the '912 patent and the '295 patent (Purdue Pharma LP, The Purdue Frederick Company, The P.F. Laboratories, Inc., The Purdue Pharma Company, v. TEVA Pharmaceuticals USA, Inc., Civil Action No. 01-CV-8507). The Agency recognizes that the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time the Agency was precluded from approving your product, has expired.

TEVA is eligible for 180-day generic drug exclusivity for Oxycodone Hydrochloride Extended-release Tablets, 80 mg, as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. This is because the agency has concluded that TEVA was the first ANDA applicant to submit a substantially complete ANDA for Oxycodone Hydrochloride Extended-release Tablets, 80 mg, containing paragraph IV certifications to each patent listed in the "Orange Book". This exclusivity will begin to run from the date TEVA begins commercial marketing of the drug product, or upon the decision of a court holding the patents which were the subjects of the paragraph IV certifications to be invalid or not infringed; whichever event occurs first.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patents invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 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 FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 3/23/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
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APPLICATION NUMBER:

76-168

**TENTATIVE APPROVAL
LETTER(S)**

SEP 29 2003

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 8, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxycodone Hydrochloride Extended-release Tablets, 80 mg.

Reference is also made to your amendments dated May 5, and July 2, 2003. We also refer to your communications dated August 3, and November 15, 2001, addressing patent issues noted below.

We have completed the review of this abbreviated application and based upon the information you have presented to date, we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time due to the ongoing patent litigation issues explained below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, OxyContin Controlled-release Tablets, 80 mg, of Purdue Pharma LP, is subject to multiple periods of patent protection. As noted in the agency's publication entitled Approved Drug

Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. patents 4,861,598 (the '598 patent), and 4,970,075 (the '075 patent) are scheduled to expire on August 29, 2006; U.S. patents 5,266,331 (the '331 patent), 5,549,912 (the '912 patent), and 5,656,295 (the '295 patent) are scheduled to expire on October 26, 2007; and U.S. patent 5,508,042 (the '042 patent) is scheduled to expire on April 16, 2013. Your application contains a paragraph IV certification to each of these patents under Section 505(j)(2)(A)(IV) of the Act stating the patents are invalid, unenforceable, and that your manufacture, use, or sale of Oxycodone Hydrochloride Extended-release Tablets, 80 mg, will not infringe on any of these patents. Section 505(j)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This action must be brought against TEVA prior to the expiration of forty-five (45) days from the date the notice TEVA provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, patent infringement actions were filed against TEVA involving challenges to the '912, '042, and '295 patents. Litigation involving these three patents is currently underway in the United States District Court for the Southern District of New York (Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc., The Purdue Pharma Company, v. TEVA Pharmaceuticals USA, Inc., Civil Action No. 01-CV-8507). Therefore, final approval for this ANDA cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
- b. the date of a court decision on the contested patents [505(j)(5)(B)(iii)(I), (II), or (III)], or
- c. all listed patents have expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate this application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED 90 days prior to the date you believe the application will be eligible for final approval. This amendment should include a justification for why you believe the application should be approved including, if necessary:

1. A copy of a final order or judgement, settlement agreement between the parties, licensing agreement between you and the patent holder, or any other relevant information, and
2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
b. a statement that no such changes have been made to the application since the date of tentative approval.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information requested above. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of their receipt. The submission of multiple amendments prior to approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under

section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be listed in the "Orange Book."

For further information on the status of this application, or prior to your submission of additional amendments, please contact Ted Palat, Pharm.D., Project Manager, at 301-594-0338, for further instructions.

Sincerely yours,



Gary Buehler

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

9/29/03

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

FINAL PRINTED LABELING

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

Rx only

WARNING:

Oxycodone hydrochloride extended-release tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

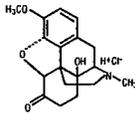
Oxycodone hydrochloride extended-release tablets are **NOT** intended for use as a pm analgesic.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets **ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY**. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone Hydrochloride Extended-Release Tablets are an opioid analgesic supplied in 80 mg tablet strength for oral administration. The tablet strength describes the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



The chemical formula is 4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C blue #2 indigo carmine lake, hydroxypropylcellulose (2208, 100M), iron oxide yellow, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydrocodone, pentamyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release tablets overdose (See OVERDOSAGE).

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration - Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation."

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration - Adverse Experience Relationships

Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSE AND ADMINISTRATION**) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics and Metabolism

The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide extended delivery of oxycodone over 12 hours.

Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the extended delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24 to 36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The

oxycodone from oxycodone hydrochloride extended-release tablets, steady-state plasma concentrations of oxycodone are achieved within 24 to 36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max} and similar for C_{min} (trough concentrations). There was less fluctuation in plasma concentrations for the oxycodone hydrochloride extended-release tablets than for the immediate-release formulation.

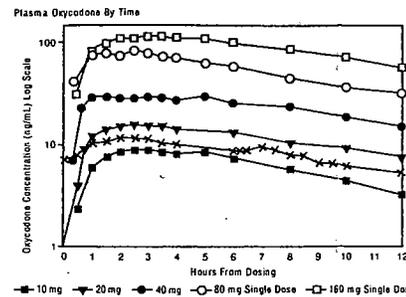


Table 1
Mean (% coefficient variation)

Regimen	Dosage Form	AUC (ng-hr/mL) [†]	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

[†] for single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}
* data obtained while volunteers received naltrexone which can enhance absorption

Table 2
Mean (% coefficient variation)

Regimen	Dosage Form	AUC (ng-hr/mL) [†]	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets	1935.3 [34.7]	152.0 [28.9]	1.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets	1859.3 [30.1]	153.4 [25.1]	1.78 [69.3]	n.a.
	1 x 160 mg oxycodone hydrochloride extended-release tablets	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

[†] for single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}
* data obtained while volunteers received naltrexone which can enhance absorption

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 93% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets.

Distribution

Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone <14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in excretion but

represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs if amiodarone and quinidine as well as polycyclic anti-depressants). However, study involving 10 subjects using quinidine, a known inhibitor of cytochrome 2D6, the pharmacodynamic effects of oxycodone were unchanged.

INDICATIONS AND USAGE

Oxycodone hydrochloride extended-release tablets are an extended-release formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are **NOT** intended for use as a pm analgesic.

Physicians should individualize treatment in every case, initiating therapy appropriate point along a progression from non-opioid analgesics, such as steroid anti-inflammatory drugs and acetaminophen to opioids in a plan management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care and Research), the Federation of State Medical Boards Model Guidelines American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for use in the immediate post-operative period (the first 12 to 24 hours following surgery) if the pain is mild, or not expected to persist for an extended period. Oxycodone hydrochloride extended-release tablets are only indicated for use if the patient is already receiving the drug prior to surgery post-operative use is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from oral to oral analgesics as appropriate. (See **American Pain Society Guidelines**.)

CONTRAINDICATIONS

Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioid contraindicated. This includes patients with significant respiratory depression unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is at risk of having paralytic ileus.

WARNING: OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS CAN LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to oxycodone. Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use in opioid tolerant patients requiring daily oxycodone equivalent dosages of 80 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the person for whom it was prescribed, as such inappropriate use may have severe consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought after by abusers and people with addiction disorders and are subject to criminal diversion. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported abused by crushing, chewing, snorting, or injecting the dissolved powder practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNING: DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the management of pain. The development of addiction to opioid analgesics in managed patients with pain has been reported to be rare. However, data available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensure or State Controlled Substances Authority for information on how to pre-empt abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Oxycodone hydrochloride extended-release tablets are a mu-agonist with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug tactics include emergency calls or visits near the end of office hours, undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (obtaining additional prescriptions is common among drug abusers and people suffering untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. If abuse of opioids can occur in the absence of true addiction and is characterized by non-medical purposes, often in combination with other substances, Oxycodone hydrochloride extended-release tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescription information, including quantity, frequency, and renewal requests is advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets are intended for use only. Abuse of the crushed tablet poses a hazard of overdose and death: risk is increased with concurrent abuse of alcohol and other substances. Parenteral abuse, the tablet excipients can be expected to result in local necrosis, infection, pulmonary granulomas, and increased risk of embolism and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid analgesics. Respiratory depression is a particular problem in elderly or debilitated patients usually following large initial doses in non-tolerant patients, or when given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant obstructive pulmonary disease or cor pulmonale, and in patients having a decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone decrease respiratory drive to the point of apnea. In these patients alternative analgesics should be considered, and opioids should be employed only under medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention, secondary elevation of cerebrospinal fluid pressure, and may be markedly enhanced in the presence of head injury, intracranial lesions, or other sources of increased intracranial pressure. Oxycodone produces effects on response and consciousness which may obscure neurologic signs increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent use with drugs such as phenothiazines or other agents which compromise the body's ability to regulate circulatory function. This is accompanied by an increase in excretion but

APPROVED
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Iss. 6/2003
0033
OXYCODONE
HYDROCHLORIDE EXTENDED-
RELEASE TABLETS,
80 mg
Rx only

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MAR 23 2004

HYDROCODONE EXTENDED-RELEASE TABLETS 80 mg only

Iss. 6/2003

0033

APPROVED

...for an extended period of time.

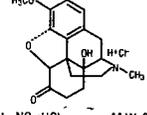
Oxycodone hydrochloride extended-release tablets are NOT intended for use as a pm analgesic.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone Hydrochloride Extended-Release Tablets ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone Hydrochloride Extended-Release Tablets are an opioid analgesic supplied in 80 mg tablet strength for oral administration. The tablet strength describes the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



C₁₈H₂₁NO₄·HCl M.W. 351.82

The chemical formula is 4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C blue #2 indigo carmine lake, hypromellose (2208, 100M), iron oxide yellow, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release tablets overdose (See OVERDOSAGE).

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration - Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent opioid analgesics. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration - Adverse Experience Relationships

Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics and Metabolism

The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide extended delivery of oxycodone over 12 hours.

Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the extended delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24 to 36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride extended-release tablets was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t_{1/2} of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, oxycodone hydrochloride extended-release tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of

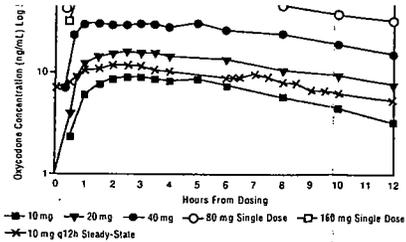


Table 1: Mean (% coefficient variation) for various regimens and dosage forms. Columns include Regimen, Dosage Form, AUC (ng-hr/mL), C_{max} (ng/mL), T_{max} (hrs), and Trough Conc. (ng/mL). Rows include Single Dose (10 mg, 20 mg, 40 mg, 80 mg) and Multiple Dose (10 mg q12h, 5 mg immediate-release q6h).

† for single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}; * data obtained while volunteers received naloxone which can enhance absorption

Table 2: Mean (% coefficient variation) for various regimens and dosage forms. Columns include Regimen, Dosage Form, AUC_{0-12h}† (ng-hr/mL), C_{max} (ng/mL), T_{max} (hrs), and Trough Conc. (ng/mL). Rows include Single Dose (4 x 40 mg, 2 x 80 mg, 1 x 160 mg) and Multiple Dose (2 x 80 mg q12h).

† for single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}; * data obtained while volunteers received naloxone which can enhance absorption

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets.

Distribution

Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone <14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t_{1/2} of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t_{1/2} elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which

steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency I Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in immediate post-operative period (the first 12 to 24 hours following surgery), or the pain is mild, or not expected to persist for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if it post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Oxycodone hydrochloride extended-release tablets are contraindicated in patient with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspect of having paralytic ileus.

WARNINGS

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 n or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medic consequences including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. The practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS or DRUG ABUSE AND ADDICTION).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent or detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects that cause in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purpose and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeker tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescription, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioid have been diverted for non-medical use. Careful record-keeping of prescriber information, including quantity, frequency, and renewal requests is strong advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets are intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. The risk is increased with concurrent abuse of alcohol and other substances. Will parental abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient. Oxycodone hydrochloride extended-release tablets, as with all opioid agonist extended-release tablets, are a particular problem in elderly or debilitated patient usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantial decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypertensive Effect

Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patient. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

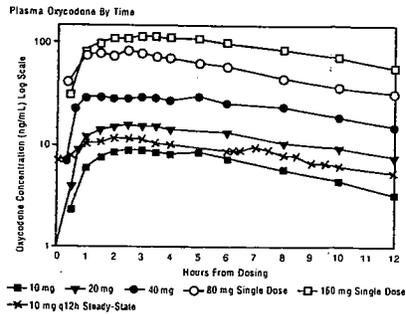
PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient population especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of oxycodone hydrochloride extended-release tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison disease); CNS depression or coma; delirium tremens; debilitated patient

oxycodone from oxycodone hydrochloride extended-release tablets, steady-state plasma concentrations of oxycodone are achieved within 24 to 36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max} and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the oxycodone hydrochloride extended-release tablets than for the immediate-release formulation.



Regimen	Dosage Form	AUC (ng·hr/mL) ^a	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets ^b	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

^a For single-dose AUC-AUC_{0-12h}, for multiple-dose AUC-AUC_{0-12h}.
^b data obtained while volunteers received naltrexone which can enhance absorption

Regimen	Dosage Form	AUC _{0-12h} (ng·hr/mL) ^a	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets	1859.3 [30.1]	153.4 [25.1]	1.78 [69.3]	n.a.
	1 x 160 mg oxycodone hydrochloride extended-release tablets	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

^a For single-dose AUC-AUC_{0-12h}, for multiple-dose AUC-AUC_{0-12h}.
^b data obtained while volunteers received naltrexone which can enhance absorption

OXycodone Hydrochloride Extended-Release Tablets are NOT Indicated for Rectal Administration. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects
Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets.

Distribution
Following intravenous administration, the volume of distribution (V_{dss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism
Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.5 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion
Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 13%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone <14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations
Elderly
The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment
Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in excretion but

represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

INDICATIONS AND USAGE
Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society Guidelines.)

CONTRAINDICATIONS
Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS
OXycodone Hydrochloride Extended-Release Tablets are to be SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXycodone Hydrochloride Extended-Release Tablets could lead to the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids
Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS and DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse
Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION
Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioids, have been misused for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets are intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parental abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression
Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury
The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect
Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor

tone. Hypotension associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants
Oxycodone hydrochloride extended-release tablets should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of oxycodone hydrochloride extended-release tablets.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Amputation Surgery and Post-Operative Use
Oxycodone hydrochloride extended-release tablets are not indicated for pre-operative analgesia (administration pre-operatively for the management of post-operative pain).

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society Guidelines).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs in use, and the temporary changes in physiology caused by the surgical intervention (see **DOSSAGE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release tablets and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease
Oxycodone may cause a spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence
Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers (see PATIENT INFORMATION at the end of the package insert)

If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release tablets without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of oxycodone and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be instructed to keep oxycodone hydrochloride extended-release tablets in a secure place out of the reach of children. When oxycodone hydrochloride extended-release tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride extended-release tablets are an opioid with no approved use in the management of addictive disorders. Their proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including oxycodone hydrochloride extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone hydrochloride extended-release tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

tablets are an opioid agonist and its liability similar to morphine.

tablets are an extended-release formulation for the management of around-the-clock analgesic use.

tablets are NOT intended for use as a prn analgesic.

0 mg tablets ARE FOR USE IN ENGLISH may cause fatal respiratory depression if exposed to opioids.

PLEASE TABLETS ARE TO BE KEEN, CHEWED, OR CRUSHED. OXycodone Hydrochloride Extended-Release and Absorption IE.

tablets are an opioid analgesic. The tablet strength as the hydrochloride salt. The as follows:

W. 351.82 -methoxy-17-methylmorphinan-

derived from the opium alkaloid, water (1 g in 5 to 7 mL). It is a coefficient 0.7). Each tablet contains the dioxide, FD&C blue #2 indigo yellow, lactose anhydrous, crystalline cellulose, polyethylene

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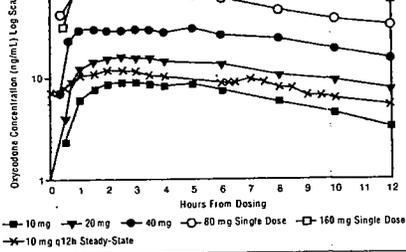


Table 1
Mean [% coefficient variation]

Regimen	Dosage Form	AUC _{0-12h} (ng·hr/mL)	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

† For single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}. * data obtained while volunteers received naloxone which can enhance absorption

Table 2
Mean [% coefficient variation]

Regimen	Dosage Form	AUC _{0-12h} (ng·hr/mL)	C _{max} (ng/mL)	T _{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg oxycodone hydrochloride extended-release tablets	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† For single-dose AUC=AUC_{0-12h}; for multiple-dose AUC=AUC_{0-12h}. * data obtained while volunteers received naloxone which can enhance absorption

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects
Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets.

Distribution
Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism
Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion
Oxycodone and its metabolites are excreted primarily via the kidney. The amounts excreted in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations
Elderly
The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment
Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in 1/2 of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment
Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The 1/2 elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see PRECAUTIONS)
Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone and

steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parental to oral analgesics as appropriate. (See **American Pain Society Guidelines**.)

CONTRAINDICATIONS
Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids
Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing, snorting, or injecting the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS AND DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse
Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION
Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, drug for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets are intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression
Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea in these patients. Alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury
The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect
Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients.

Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS
General
Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of oxycodone hydrochloride extended-release tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients;

the usual doses of oxycodone hydrochloride extended-release tablets.
Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Antagonist/agonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use
Oxycodone hydrochloride extended-release tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parental to oral analgesics as appropriate (see **American Pain Society Guidelines**).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release tablets and other morphine-like opioids have been shown to decrease bowel motility, ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease
Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence
Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and malaise. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers (see PATIENT INFORMATION at the end of the package insert)

If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release tablets without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be instructed to keep oxycodone hydrochloride extended-release tablets in a secure place out of the reach of children. When oxycodone hydrochloride extended-release tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction
Oxycodone hydrochloride extended-release tablets are an opioid with no approved use in the management of addictive disorders. Their proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions
Opioid analgesics, including oxycodone hydrochloride extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants
Oxycodone hydrochloride extended-release tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg; chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL, and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy
Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits for oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
 Oxycodone hydrochloride extended-release tablets are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers
 Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use
 Safety and effectiveness of oxycodone hydrochloride extended-release tablets have not been established in pediatric patients below the age of 18. It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.

Geriatric Use
 In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see PHARMACOKINETICS AND METABOLISM). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release tablets. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring
 Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment
 A study of oxycodone hydrochloride extended-release tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment
 In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences
 In pharmacokinetic studies, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS
 The safety of oxycodone hydrochloride extended-release tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day. Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablets in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release tablets therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release tablets with immediate-release oxycodone and placebo, revealed a similar adverse event profile between oxycodone hydrochloride extended-release tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

	Oxycodone Hydrochloride Extended-Release Tablets (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	23	26	7
Nausea	23	27	11
Somnolence	23	24	4
Dizziness	13	16	9
Pruritus	12	14	2
Vomiting	11	12	7
Headache	7	8	7
Dry Mouth	6	7	2
Asthenia	6	7	—
Sweating	5	6	—

The following adverse experiences were reported in oxycodone hydrochloride extended-release tablets treated patients with an incidence between 1% and 5%. In descending order of frequency they were: anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post marketing experience:

- General:** accidental injury, chest pain, facial edema, malaise, neck pain, pain
- Cardiovascular:** migraine, syncope, vasodilation, ST depression
- Digestive:** dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus
- Hemic and Lymphatic:** lymphadenopathy
- Metabolic and Nutritional:** dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst
- Nervous:** abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hyposthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures
- Respiratory:** cough increased, pharyngitis, voice alteration
- Skin:** dry skin, exfoliative dermatitis, urticaria
- Special Senses:** abnormal vision, taste perversion
- Urogenital:** amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria,

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. The patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSE AND ADMINISTRATION
General Principles
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE.

OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are indicated for the management of moderate to severe pain requiring treatment with a strong opioid for continuous, around-the-clock analgesia for an extended period of time. The extended-release nature of the formulation allows the oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See BOXED WARNINGS].

Initiation of Therapy
 It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

1. the general condition and medical status of the patient;
2. the daily dose, potency and kind of the analgesic(s) the patient has been taking;
3. the reliability of the conversion estimate used to calculate the dose of oxycodone;
4. the patient's opioid exposure and opioid tolerance (if any);
5. special safety issues associated with conversion to oxycodone hydrochloride extended-release tablets doses at or exceeding 160 mg q12h (see Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg); and
6. the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

For initiation of oxycodone hydrochloride extended-release tablets therapy for patients previously taking opioids, the conversion ratios from Foley, KM, (NEJM, 1985; 313:84-95), found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.
3. Round down to a dose which is appropriate for the tablet strength available (80 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablets therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4
Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*
 (Mg/Day Prior Opioid × Factor = Mg/Day Oral Oxycodone)

Opioid	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for all high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets

Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release tablets should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naïve, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain) with the regular use of no more than two doses of supplemental analgesia per 24 hours. Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose should be reduced. If this adjustment leads to inadequate analgesia, a supplemental

analgesic should be given in the presence of this tablet strength. A physician should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Supplemental Analgesia
 Most patients given around-the-clock therapy with extended-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy
 The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy
 When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids
 To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING
 Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED
 Oxycodone Hydrochloride Extended-Release Tablets, 80 mg are green, film-coated, oval, convex tablets debossed with "33" on one side and "33" on the other side. They are available in bottles of 100.

Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION
DEA Order Form Required.

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

Read this information carefully before you take oxycodone hydrochloride extended-release tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if oxycodone hydrochloride extended-release tablets are right for you. Share the important information in this leaflet with members of your household.

What Is the Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- Use oxycodone hydrochloride extended-release tablets the way your doctor tells you to.
- Use oxycodone hydrochloride extended-release tablets only for the condition for which it was prescribed.
- Oxycodone hydrochloride extended-release tablets are not for occasional ("as needed") use.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew them before swallowing. Oxycodone hydrochloride extended-release tablets work properly over 12 hours only when swallowed whole. If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.
- Keep oxycodone hydrochloride extended-release tablets out of the reach of children. Accidental overdose by a child is dangerous and may result in death.
- Prevent theft and misuse. Oxycodone hydrochloride extended-release tablets contain a narcotic pillbiter that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone hydrochloride extended-release tablets come in several strengths and contain the medicine oxycodone (ox-KOe-done). This medicine is a painkiller like morphine. Oxycodone hydrochloride extended-release tablets treat moderate to severe pain that is expected to last for an extended period of time. Use oxycodone hydrochloride extended-release tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take oxycodone hydrochloride extended-release tablets if

- your doctor did not prescribe oxycodone hydrochloride extended-release tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox®, Tylenol with Codeine®, or Vicodin®). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 to 24 hours ago and you were not taking oxycodone hydrochloride extended-release tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if oxycodone hydrochloride extended-release tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking oxycodone hydrochloride extended-release tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone hydrochloride extended-release tablets may not be right for you. Tell your doctor if you are breastfeeding. Oxycodone hydrochloride extended-release tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with oxycodone hydrochloride extended-release tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- Follow your doctor's directions exactly. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take oxycodone hydrochloride extended-release tablets more often than prescribed.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.

What are the Possible Side Effects?

- Do not drive, operate machinery, or engage in dangerous activities. Oxycodone hydrochloride extended-release tablets may make you feel drowsy.
- Do not take alcohol with tablets. It may increase drowsiness.
- Do not take other medications without prescription and be especially careful at night.

What are the Possible Side Effects?

- Call your doctor or get medical help if you experience any of the following:
 - your breathing slows or stops
 - you feel faint, dizzy, or confused

Some of the common side effects are nausea, vomiting, sweating, weakness, and hiccups.

There is a risk of abuse or addiction. If you are taking drugs in the past, you may have withdrawal symptoms when you stop taking oxycodone hydrochloride extended-release tablets. For a complete list of possible side effects, see the full prescribing information.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use oxycodone hydrochloride extended-release tablets if you are pregnant or plan to become pregnant.
- Do not give oxycodone hydrochloride extended-release tablets to children.
- Store oxycodone hydrochloride extended-release tablets in a secure place, to protect them from theft.
- Store oxycodone hydrochloride extended-release tablets in a secure place, to protect them from theft.

This leaflet summarizes oxycodone hydrochloride extended-release tablets. It is not a substitute for the information on this product that you should read carefully.

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Vicodin is a brand name of Oxycodone Hydrochloride Extended-Release Tablets.

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Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness in pediatric patients with oxycodone hydrochloride extended-release tablets have not been established in pediatric patients below the age of 18. It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see PHARMACOKINETICS AND METABOLISM). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release tablets. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of oxycodone hydrochloride extended-release tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of oxycodone hydrochloride extended-release tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablets in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release tablets therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release tablets with immediate-release oxycodone and placebo, revealed a similar adverse event profile between oxycodone hydrochloride extended-release tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

Table 3

	Oxycodone Hydrochloride Extended-Release Tablets (n=227)	Immediate-Release (n=225)	Placebo (n=45)
Constipation	23	26	7
Nausea	23	27	11
Somnolence	23	24	4
Dizziness	13	16	9
Pruritus	13	12	2
Vomiting	12	14	7
Headache	7	8	7
Dry Mouth	6	7	2
Asthenia	6	7	—
Sweating	5	6	2

The following adverse experiences were reported in oxycodone hydrochloride extended-release tablets treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post marketing experience:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hyposthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, timidity, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: aménorrhoea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of oxycodone hydrochloride extended-release tablets, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when oxycodone hydrochloride extended-release tablets are abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are indicated for the management of moderate to severe pain requiring treatment with a strong opioid for continuous, around-the-clock analgesia for an extended period of time. The extended-release nature of the formulation allows the oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM). While symmetric (same dose AM and PM) around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (See BOXED WARNINGS).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

1. the general condition and medical status of the patient;
2. the daily dose, potency and kind of the analgesic(s) the patient has been taking;
3. the reliability of the conversion estimate used to calculate the dose of oxycodone;
4. the patient's opioid exposure and opioid tolerance (if any);
5. special safety issues associated with conversion to oxycodone hydrochloride extended-release tablets doses at or exceeding 160 mg q12h (see Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg); and
6. the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

For initiation of oxycodone hydrochloride extended-release tablets therapy for patients previously taking opioids, the conversion ratios from Foley, KM. (NEJM, 1965; 313:94-95), found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.
3. Round down to a dose which is appropriate for the tablet strength available (80 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablets therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*
(Mg/Day Prior Opioid × Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codaine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets

Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release tablets should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naïve, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain) with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg (For use in opioid-tolerant patients only)

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg

to be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

Oxycodone Hydrochloride Extended-Release Tablets, 80 mg are green, film-coated, oval, convex tablets debossed with "93" on one side and "33" on the other side. They are available in bottles of 100.

Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION

DEA Order Form Required.

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

Read this information carefully before you take oxycodone hydrochloride extended-release tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if oxycodone hydrochloride extended-release tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- Use oxycodone hydrochloride extended-release tablets the way your doctor tells you to.
- Use oxycodone hydrochloride extended-release tablets only for the condition for which it was prescribed.
- Oxycodone hydrochloride extended-release tablets are not for occasional ("as needed") use.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew them before swallowing. Oxycodone hydrochloride extended-release tablets work properly over 12 hours only when swallowed whole. If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.
- Keep oxycodone hydrochloride extended-release tablets out of the reach of children. Accidental overdose by a child is dangerous and may result in death.
- Prevent theft and misuse. Oxycodone hydrochloride extended-release tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone hydrochloride extended-release tablets come in several strengths and contain the medicine oxycodone (ox-codone). This medicine is a painkiller like morphine. Oxycodone hydrochloride extended-release tablets treat moderate to severe pain that is expected to last for an extended period of time. Use oxycodone hydrochloride extended-release tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

- Do not take oxycodone hydrochloride extended-release tablets if**
- your doctor did not prescribe oxycodone hydrochloride extended-release tablets for you.
 - your pain is mild or will go away in a few days.
 - your pain can be controlled by occasional use of other painkillers.
 - you have severe asthma or severe lung problems.
 - you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox[®], Tylenol with Codeine[®], or Vicodin[™]). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
 - you had surgery less than 12 to 24 hours ago and you were not taking oxycodone hydrochloride extended-release tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if oxycodone hydrochloride extended-release tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below.

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking oxycodone hydrochloride extended-release tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone hydrochloride extended-release tablets may not be right for you. Tell your doctor if you are breast feeding. Oxycodone hydrochloride extended-release tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with oxycodone hydrochloride extended-release tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

• Follow your doctor's directions exactly. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take oxycodone hydrochloride extended-release tablets more often than prescribed.

• Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.

• If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.

• In case of overdose, call your local emergency number or poison control center right away.

• Review your pain regularly with your doctor to determine if you still need oxycodone hydrochloride extended-release tablets.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping oxycodone hydrochloride extended-release tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking oxycodone hydrochloride extended-release tablets all at once if you have been taking it for more than a few days.

After you stop taking oxycodone hydrochloride extended-release tablets, flush the unused tablets down the toilet.

• you feel faint, dizzy, confused.

Some of the common side effects tablets are nausea, vomiting, dizziness, sweating, weakness, and headache continued use.

There is a risk of abuse or addiction drugs in the past, you may have a again while using oxycodone hydrochloride how often patients with continue but the risk has been reported to be

These are not all the possible side effects tablets. For a complete list, ask your

General Advice About Oxycodone

- Do not use oxycodone hydrochloride for which it was not prescribed
- Do not give oxycodone hydrochloride even if they have the same symptoms cause severe medical problem
- Store oxycodone hydrochloride temperature, between 20° and 25°C

This leaflet summarizes the most important information about oxycodone hydrochloride extended-release tablets with your doctor. Also, you can learn about oxycodone hydrochloride extended-release tablets from your doctor.

*Tylox and Tylenol with Codeine are trademarks of Parke-Davis Pharmaceutical Company.
**Vicodin is a brand name of BBL



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Some opioid antagonists such as naloxone or nalmefene are specific antidotes that reverse the effects of opioid overdose. Opioid antagonists should be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid agonist for details of their proper use.

USE AND ADMINISTRATION
Oral Principles
CODEONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE AN OPIOID ANALGESIC AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE POTENTIAL SIMILAR TO MORPHINE.
CODEONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.
CODEONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE TAKEN AS A WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. IF BROKEN, CHEWED OR CRUSHED, CODEONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

It is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment. Oxycodone hydrochloride extended-release tablets are indicated for the management of moderate to severe pain requiring treatment with a strong opioid for continuous, around-the-clock analgesia for an extended period of time. The extended-release formulation allows the oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see CLINICAL PHARMACOLOGY: PHARMACOKINETICS AND METABOLISM). While symmetric (same dose AM and PM) around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient on only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management as outlined by the World Health Organization, the American Pain Society and Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (See **BOXED WARNINGS**).

Initiation of Therapy
 • critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

- the general condition and medical status of the patient;
- the daily dose, potency and kind of the analgesic(s) the patient has been taking;
- the reliability of the conversion estimate used to calculate the dose of oxycodone;
- the patient's opioid exposure and opioid tolerance (if any);
- special safety issues associated with conversion to oxycodone hydrochloride extended-release tablets doses at or exceeding 160 mg q12h (see Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg); and
- the balance between pain control and adverse experiences.

A patient should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS depressant medications (see **PRECAUTIONS: Drug-Drug Interactions**).

When initiating oxycodone hydrochloride extended-release tablets therapy for patients previously taking opioids, the conversion ratios from Fentanyl, KM, (MEJM, S; 313:84-95), found below, are a reasonable starting point, although not verified well-controlled, multiple-dose trials.

Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

When converting from oxycodone, divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.

Round down to a dose which is appropriate for the tablet strength available (80 mg tablets).

Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablets therapy is initiated.

No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4
Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*
(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
codeine	1	—
fentanyl	0.15	—
furoxodone	0.9	—
promorphone	4	20
orphanol	7.5	15
peridine	0.1	0.4
thadone	1.5	3
rhine	0.5	3

It is used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for h-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets

Within 15 minutes following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release tablets should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very little clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences
 In patients receiving opioids, especially those who are opioid-naïve, will experience adverse effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse effects such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage
 Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain) with the regular use of no more than two doses of supplemental analgesia per 24 hours. Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximately reached within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is clinical information on dosing intervals shorter than q12h. As a guideline, the q12h dose may be increased from 10 mg to 20 mg q12h, the total daily oxycodone dose may be increased by 25% to 50% of the current dose at each increase.

Signs of excessive opioid-related adverse experiences are observed, the next dose should be reduced. If this adjustment leads to inadequate analgesia, a combination

of oral and parenteral analgesics should be taken in the prescribing information. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Supplemental Analgesia
 Most patients given around-the-clock therapy with extended-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy
 The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy
 When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids
 To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING
 Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED
 Oxycodone Hydrochloride Extended-Release Tablets, 80 mg are green, film-coated, oval, convex tablets debossed with "93" on one side and "33" on the other side. They are available in bottles of 100.

Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). Dispense in a light, tight-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION
DEA Order Form Required.

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

Read this information carefully before you take oxycodone hydrochloride extended-release tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if oxycodone hydrochloride extended-release tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- Use oxycodone hydrochloride extended-release tablets the way your doctor tells you to.
- Use oxycodone hydrochloride extended-release tablets only for the condition for which it was prescribed.
- Oxycodone hydrochloride extended-release tablets are not for occasional ("as needed") use.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew them before swallowing. Oxycodone hydrochloride extended-release tablets work properly over 12 hours only when swallowed whole. If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.
- Keep oxycodone hydrochloride extended-release tablets out of the reach of children. Accidental overdose by a child is dangerous and may result in death.
- Prevent theft and misuse. Oxycodone hydrochloride extended-release tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone hydrochloride extended-release tablets come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone hydrochloride extended-release tablets treat moderate to severe pain that is expected to last for an extended period of time. Use oxycodone hydrochloride extended-release tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take oxycodone hydrochloride extended-release tablets if

- your doctor did not prescribe oxycodone hydrochloride extended-release tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox™, Tylenol with Codeine™, or Vicodin™). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 to 24 hours ago and you were not taking oxycodone hydrochloride extended-release tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if oxycodone hydrochloride extended-release tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking oxycodone hydrochloride extended-release tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone hydrochloride extended-release tablets may not be right for you. Tell your doctor if you are breast feeding. Oxycodone hydrochloride extended-release tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with oxycodone hydrochloride extended-release tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- Follow your doctor's directions exactly. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take oxycodone hydrochloride extended-release tablets more often than prescribed.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities until you know how you react to this medicine. Oxycodone hydrochloride extended-release tablets can make you sleepy.
- Do not drink alcohol while using oxycodone hydrochloride extended-release tablets. It may increase the chance of getting dangerous side effects.
- Do not take other medicines without your doctor's approval. Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of oxycodone hydrochloride extended-release tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using oxycodone hydrochloride extended-release tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of oxycodone hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use oxycodone hydrochloride extended-release tablets for conditions for which it was not prescribed.
- Do not give oxycodone hydrochloride extended-release tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.
- Store oxycodone hydrochloride extended-release tablets at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP).

This leaflet summarizes the most important information about oxycodone hydrochloride extended-release tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about oxycodone hydrochloride extended-release tablets that is written for health professionals.

*Tylox and Tylenol with Codeine are brand names of ORTHO-MCNEIL PHARMACEUTICAL.

**Vicodin is a brand name of ABBOTT-LABORATORIES.

Manufactured By:
TEVA PHARMACEUTICALS USA
 Sellersville, PA 18960

Iss. 6/2003



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APPROVED

TEVA PHARMACEUTICALS, USA
Salesville, Ohio

Iss. 6/2003

KEEP OUT OF REACH OF CHILDREN. MEDICATION OUT OF THE REACH OF CHILDREN.

Dispense in child-resistant container as required.

Store at 20° to 25° (68° to 77°) (see USP).

Do not use if the seal is broken. See package insert for full prescribing information. Swallow whole.

NDC 0093-0033-01

**OXYCODONE
HYDROCHLORIDE
EXTENDED-RELEASE
TABLETS
80 mg**

Each film-coated tablet contains:
Oxycodone hydrochloride 80 mg
For use only in OPIAT PATIENTS
Rx only

MAR 23 2004

TEVA

PATIENT INFORMATION



OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

Read this information carefully before you take oxycodone hydrochloride extended-release tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if oxycodone hydrochloride extended-release tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information You Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- Use oxycodone hydrochloride extended-release tablets the way your doctor tells you.
- Use oxycodone hydrochloride extended-release tablets only for the condition for which they are prescribed.
- Oxycodone hydrochloride extended-release tablets are not for occasional ("as needed") use.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew them before swallowing. Oxycodone hydrochloride extended-release tablets work properly over 12 hours only when swallowed whole. If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.
- Keep oxycodone hydrochloride extended-release tablets out of the reach of children. Accidental overdose by a child is dangerous and may result in death.
- Prevent theft and misuse. Oxycodone hydrochloride extended-release tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What Are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone hydrochloride extended-release tablets come in several strengths and contain the medicine oxycodone (ox-KOE-done). This medicine is a painkiller like morphine. Oxycodone hydrochloride extended-release tablets treat moderate to severe pain that is expected to last for an extended period of time. Use oxycodone hydrochloride extended-release tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

- Do not take oxycodone hydrochloride extended-release tablets if**
- your doctor did not prescribe oxycodone hydrochloride extended-release tablets for you.
 - your pain is mild or will go away in a few days.
 - your pain can be controlled by occasional use of other painkillers.
 - you have severe asthma or severe lung problems.
 - you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox[®], Tylenol with Codeine[®], or Vicodin[®]). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
 - you had surgery less than 12 to 24 hours ago and you were not taking oxycodone hydrochloride extended-release tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if oxycodone hydrochloride extended-release tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below.

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking oxycodone hydrochloride extended-release tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone hydrochloride extended-release tablets may not be right for you. Tell your doctor if you are breast feeding. Oxycodone hydrochloride extended-release tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with oxycodone hydrochloride extended-release tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- Follow your doctor's directions exactly. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take oxycodone hydrochloride extended-release tablets more often than prescribed.
- Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- In case of overdose, call your local emergency number or poison control center right away.
- Review your pain regularly with your doctor to determine if you still need oxycodone hydrochloride extended-release tablets.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping oxycodone hydrochloride extended-release tablets: Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking oxycodone hydrochloride extended-release tablets all at once if you have been taking it for more than a few days.

After you stop taking oxycodone hydrochloride extended-release tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities until you know how you react to this medicine. Oxycodone hydrochloride extended-release tablets can make you sleepy.
- Do not drink alcohol while using oxycodone hydrochloride extended-release tablets. It may increase the chance of getting dangerous side effects.
- Do not take other medicines without your doctor's approval. Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms.

Some of the common side effects of oxycodone hydrochloride extended-release tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using oxycodone hydrochloride extended-release tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of oxycodone hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use oxycodone hydrochloride extended-release tablets for conditions for which it was not prescribed.
- Do not give oxycodone hydrochloride extended-release tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.
- Store oxycodone hydrochloride extended-release tablets at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP).

This leaflet summarizes the most important information about oxycodone hydrochloride extended-release tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about oxycodone hydrochloride extended-release tablets that is written for health professionals.

*Tylox and Tylenol with Codeine are brand names of ORTHO-MCNEIL PHARMACEUTICAL.

**Vicodin is a brand name of ABBOTT LABORATORIES.

only

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 6/2003

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

CSO LABELING REVIEW(S)

may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

c. PRECAUTIONS

See comment (a) under PATIENT INFORMATION LEAFLET

d. DOSAGE AND ADMINISTRATION

i. General Principles - Sixth paragraph, second sentence:

...allows the oxycodone tablets to be... [rather than]

ii. Initiation of Therapy - Item #1 following the paragraph "Oxycodone...side effects."

...estimates (see Table 4 below), multiply... [rather than "]

e. HOW SUPPLIED

See comment (b) under PATIENT INFORMATION LEAFLET.

Please revise your labels and labeling, as instructed above and submit in draft. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rtd/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of Patient Information Leaflet approved for Oxycontin Controlled Release Tablets

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (a) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). See comment under DESCRIPTION.
6. Patent Data

020553	001	4861598	AUG 29,2006
020553	001	4970075	NOV 13,2007
020553	001	5266331	FEB 05,2008
020553	001	5508042	APR 16,2013
020553	001	5549912	FEB 05,2008
020553	001	5656295	FEB 05,2008

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. “Dose proportionality information” (i.e., the comparison between different strengths tablets) under “CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism” has been retained including all tables per team leader's advice. This decision was made at the time of review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has been carved out.
8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. Refer to the general comment. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

10. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

11. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA – 100s for both strengths

12. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

13. SCORING – Both RLD and ANDA unscored.

14. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, cap) with Liner (p.3893, B.1.2 & p.3627, B.3.10 (160 mg))

15. RLD employees a specific delivery form of "—" tablet. ANDA proposes "—" tablets. The sponsor did not include any specific information associated with the "—" tablet.

16. Teva is the manufacturer of this drug product.

Date of Review: November 1, 2001

Date of Submission: January 11, 2001

Primary Reviewer: Chan Park

Date: 2/1/02

Team Leader: Charlie Hoppes

Date:

Chan Park
CHoppes 2/1/02

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

**APPEARS THIS WAY
ON ORIGINAL**

1.1

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-168

Date of Submission: May 8, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

Labeling Deficiencies:

1. GENERAL COMMENT

Include the phrase "[see USP]" in the storage temperature statement.

2. CONTAINER – 100s

a. See GENERAL COMMENT above.

b. We encourage the increase of prominence for the statements "Swallow tablets whole. Do not crush or chew." by printing in bold face type or any other means.

c. Please assure that the controlled substances symbol appear clear and large enough. We refer you to 21 CFR 1302.04 for guidance.

d. Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06.

3. INSERT

a. GENERAL

i. Please note that the insert labeling for the reference listed drug, OxyContin® was last approved on July 18, 2001. Please revise your insert labeling in accordance with the attached OxyContin® insert labeling. In addition, we have the following comments.

ii. It is preferable to use the term "mcg" rather than " — throughout the text.

iii. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.

iv. Revise to read "mL" rather than " — throughout the text.

v. Italicize the terms *in vivo* throughout the text.

vi. We believe that the information regarding dose proportionality for all strengths should be included in your insert labeling including the tables.

b. DESCRIPTION

i. ...4,5-Epoxy14 - ... [note upper case "E" per USP 24]

- ii. Revise the molecular weight to read "351.82" per USP 24.
- iii. We note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.*, ~~_____~~). Please revise and/or comment.
- iv. Last paragraph, last sentence – Revise to read:

Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal...

c. CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism

This is a subsection heading. Please reduce the prominence so that it is differentiated from section headings.

d. INDICATIONS AND USAGE

...tablets are an extended-release oral... [add "extended-release"]

e. HOW SUPPLIED

See GENERAL COMMENT above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rd/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of last approved innovator's insert labeling

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (d) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022). The insert labeling was last approved on July 18, 2001.
2. It is NOT a subject of a USP monograph.
3. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be inconsistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2.
5. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

6. The innovator markets 10, 20, 40, 80, and 160 mg strengths whereas the sponsor proposed only 80 mg strength. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. “Dose proportionality information” (i.e., the comparison between different strengths tablets) under “CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism” has been retained including all tables per team leader's advice. This decision was made at the time or review of ANDA 75-923 (Endo).
7. Since two tablets of 80 mg can be administered in lieu of one 160 mg tablet, we will retain any specific information pertaining to the 160 mg tablet.
8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT, See general comment.

9. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

10. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA – 100s.

11 The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.2, P.3951.

12. SCORING – Both RLD and ANDA unscored.

13. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s CRC. — cap) with Liner (p.3893, B .1.2)

14. RLD employees a specific delivery form of " — tablet. ANDA proposes — tablets. The sponsor did not include any specific information associated with the " — tablet.

15. Teva is the manufacturer of this drug product.

Date of Review: August 1, 2001

Date of Submission: May 8, 2001

Primary Reviewer: Chan Park

Date:

Team Leader: Charlie Hoppes

Date:

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)

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Review

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3-1

(This review supersedes the one prepared on 8/1/01)
VIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168

Date of Submission: May 8, 2001 and July 25, 2001

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

Include the phrase "[see USP]" in the storage temperature statement.

3-1
fatal
2. CONTAINER – 100s

- a. See GENERAL COMMENT above.
- b. We encourage the increase of prominence for the statements "Swallow tablets whole. Do not crush or chew." by printing in bold face type or any other means.
- c. Please assure that the controlled substances symbol appear clear and large enough. We refer you to 21 CFR 1302.04 for guidance.
- d. Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06.
- e. We encourage you to differentiate your drug products of different strengths by using boxing, contrasting colors, and/or some other means.

3. INSERT

a. GENERAL

- i. Please note that the insert labeling for the reference listed drug, OxyContin® was last approved on July 18, 2001. Please revise your insert labeling in accordance with the attached OxyContin® insert labeling. In addition, we have the following comments.
- ii. It is preferable to use the term "mcg" rather than "µ" throughout the text.
- iii. It is preferable to use the term "to" rather than a hyphen when expressing a numerical range.
- iv. Revise to read "mL" rather than "ml" throughout the text.
- v. Italicize the terms *in vivo* throughout the text.
- vi. We believe that the information regarding dose proportionality for all strengths should be included in your insert labeling including the tables.

b. DESCRIPTION

- i. ...4,5-Epoxy14 - ... [note upper case "E" per USP 24]
- ii. Revise the molecular weight to read "351.82" per USP 24.
- iii. We note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.*, _____). Please revise and/or comment.
- iv. Last paragraph, last sentence – Revise to read:

Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal...

c. CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism

This is a subsection heading. Please reduce the prominence so that it is differentiated from section headings.

d. INDICATIONS AND USAGE

...tablets are an extended-release oral... [add "extended-release"]

e. HOW SUPPLIED

See GENERAL COMMENT above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of last approved innovator's insert labeling

NOTES/QUESTIONS TO THE CHEMIST:

Refer to the comment (d) under CONTAINER.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022). The insert labeling was last approved on July 18, 2001.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). See comment under DESCRIPTION.
6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

7. The innovator markets 10, 20, 40, 80, and 160 mg strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time of review of ANDA 75-923 (Endo).
8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted

between 15oC (59oF) and 30oC (86oF).

ANDA: CRT, See general comment.

9. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

10. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA – 100s for both strengths

11 The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

12. SCORING – Both RLD and ANDA unscored.

13. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

14. RLD employees a specific delivery form of "_____tablet. ANDA proposes _____ tablets. The sponsor did not include any specific information associated with the "_____tablet.

15. Teva is the manufacturer of this drug product.

Date of Review: August 9, 2001

Date of Submission: May 8, 2001 & July 25, 2001

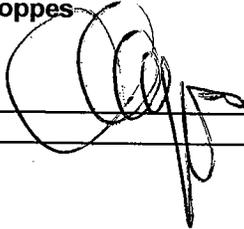
Primary Reviewer: Chan Park



Date:

8/10/01

Team Leader: Charlie Hoppes



Date:

8/10/01

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)

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Review

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-168

Date of Submission: January 11, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. GENERAL COMMENT

As addressed in the last deficiency letter, pending resolution of the Citizen Petition filed on September 18, 2001, regarding Oxycontin® (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg, we defer labeling comments specifically associated with your proposed 160 mg tablets.

2. CONTAINER – 100s

- a. We note that you did not respond to our comment "Please assure that your container systems include a tamper-evident seal. We refer you to 21 CFR 1302.06." in the last deficiency letter. Please respond.
- b. We note that you submitted your draft container labels for the 80 mg strength only. Please include your proposal for the 160 mg strength in your next submission if you are still seeking for the approval of 160 mg tablets.

3. PATIENT INFORMATION LEAFLET

- a. Please submit your proposal for this labeling piece to be in accordance with the attached patient information leaflet approved on January 15, 2002 for the reference listed drug, Oxycontin Controlled Release Tablets. In addition, describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets you will supply for each container size and how these leaflets will be supplied for dispensing to the patients.
- b. Please ensure that the full text of this patient information is also reprinted at the end of the insert labeling. In addition, this patient information must be referred to in the PRECAUTIONS, Information for Patients subsection. See 21 CFR 201.57(f)(2) for guidance.

4. INSERT

a. DESCRIPTION

As we addressed in the last deficiency letter, we note that you have not listed all inactive ingredients found in your components and composition statements (*i.e.*, _____). Please revise and/or comment.

- b. DRUG ABUSE AND ADDICTION - Include the following subsection immediately following the "Respiratory Depression" subsection.

Head Injury

Oxycodone may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone

may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

c. PRECAUTIONS

See comment (a) under PATIENT INFORMATION LEAFLET

d. DOSAGE AND ADMINISTRATION

i. General Principles - Sixth paragraph, second sentence:

...allows the oxycodone tablets to be... [rather than "]

ii. Initiation of Therapy - Item #1 following the paragraph "Oxycodone... side effects."

...estimates (see Table 4 below), multiply... [rather than "]

e. HOW SUPPLIED

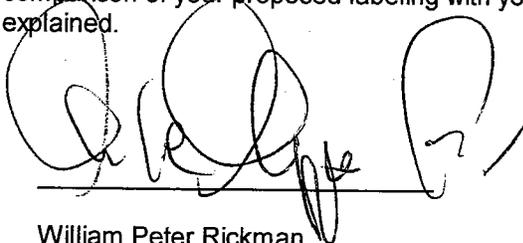
See comment (b) under PATIENT INFORMATION LEAFLET.

Please revise your labels and labeling, as instructed above and submit in draft. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: A copy of Patient Information Leaflet approved for Oxycontin Controlled Release Tablets

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-168

Date of Submission: May 7, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

Labeling Deficiencies:

1. CONTAINER – 100s
 - a. We encourage the increase of prominence for the statement "for use in opioid tolerant patients".
 - b. We encourage you to differentiate your drug products of different strengths by using boxing, contrasting colors, and/or some other means.

2. INSERT

PRECAUTIONS (Information for Patients/Caregivers) - Revise to read:

(see **PATIENT INFORMATION** at the end of the package insert)

3. PATIENT INFORMATION - How Should I Take Oxycodone Hydrochloride Extended Release Tablets?

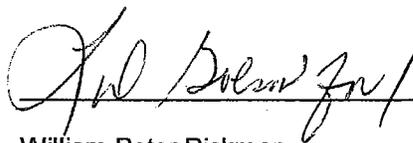
We believe that your drug product does not contain a specific delivery form of "_____ tablet" used by the innovator. Please delete the last bullet and/or comment.

Please revise your labels and labeling, as instructed above. We will not request final printed insert labeling until we are able to provide adequate response to your Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended Release Tablets, 160 mg.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). ~~_____~~ is ~~_____~~ and USP preferred name for ~~_____~~ is Triacetin.

6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. “Dose proportionality information” (i.e., the comparison between different strengths tablets) under “CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism” has been retained including all tables per team leader's advice. This decision was made at the time of review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has been carved out.
8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. Refer to the

general comment. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Parice on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170)". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn from the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). The innovator's labeling for Oxycontin still retains all information on 160 mg strength. Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA – 100s for both strengths

14. The sponsor will use the _____ manufactured by _____ to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, _____ cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

18. RLD employs a specific delivery form of "_____ tablet. ANDA proposes _____ tablets. The sponsor did not include any specific information associated with the "_____ tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: June 3, 2002

Date of Submission: May 7, 2002

Primary Reviewer: Chan Park

Date:

Acting Team Leader: Lillie Golson

Date:

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

(This AP summary supersedes the one prepared 8/8/03)
(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168

Date of Submission: February 5, 2004

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS - 100s

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 2)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 3, Rev. 6/03)

PATIENT PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 4, Rev. 6/03)

REVISIONS NEEDED POST-APPROVAL - INSERT (Adverse Reactions)

1. **Table 3:**

Add "Tablets" to the title of second column to read "Immediate-Release Tablets".

2. Revise the "General" subsection of ADVERSE REACTIONS section to read "pain, and symptoms associated with either on anaphylactic or anaphylactoid reaction" as instructed by the Agency. [Add ",and symptoms associated with either on anaphylactic or anaphylactoid reaction"]. The sponsor made a commitment to this revision in the amendment dated 2/5/04.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: OxyContin® controlled-release tablets (20-553/S-035). The insert labeling was last approved on November 20, 2003. The patient information leaflet (S-024) was approved January 15, 2002.

NDA Number: 20-553

NDA Drug Name: OxyCotin® tablets

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:

S-035/November 20, 2003 (package insert)
S-024/January 15, 2002 (patient information leaflet)

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparisons

Other Comments:

The sponsor withdrew the proposal for the 160 mg strength.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-035). The insert labeling was last approved on November 20, 2003. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength. **Then, the sponsor withdrew the proposal for the 160 mg strength in the amendment of May 5, 2003.** See FTR 8 & 10 below.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). ~~is~~ and USP preferred name for ~~is~~ is Triacetin.
6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Patent Cert.	Labeling Impact
020553	004	4861598	AUG 29,2006		IV	No
020553	004	4970075	AUG 29,2006		IV	No
020553	004	5266331	OCT 26,2007		IV	No
020553	004	5508042	APR 16,2013	U-443	IV	No
020553	004	5549912	OCT 26,2007		IV	No
020553	004	5656295	OCT 26,2007	U-443	IV	No

U-443 - Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor initially proposed only 80 mg and 160 mg strengths, but withdrew the 160 mg strength later on. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice in the past. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg has been carved out.
8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170)." However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of

discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn from the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne, Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question – is that a "safety" reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). **The innovator's labeling for Oxycontin still retains all information on 160 mg strength.** Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25°C (60-77°F); brief excursions permitted between 15°C (59°F) and 30°C (86°F).

ANDA: Container - Store at controlled room temperature, between 15° and 30°C (59° and 86°F) [see USP].

Insert Labeling - Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). See GENERAL comment above.

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA – 100s

14. The sponsor will use the _____, manufactured by _____ to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.2, P.3951(80 mg).
16. SCORING – Both RLD and ANDA unscored.
17. CONTAINER/CLOSURE
Container – HDPE
Closure – 100s (CRC, cap) with Liner (p.3893, B .1.2)
18. RLD employs a specific delivery form of ~~tablets~~ tablet. ANDA proposes ~~tablets~~ tablets. The sponsor did not include any specific information associated with the ~~tablets~~ tablet.
19. Teva is the manufacturer of this drug product.
20. The sponsor proposed one PPI per a bottle of 100 tablets. I called the firm and spoke with Mr. Philip Erickson on this proposal on August 8, 2003. He stated that their proposal is the same as the innovator's.
21. The sponsor is in the process of getting approval for the Risk Management Program. It was submitted per the new drug division to follow the lead of the innovator and is currently under review by the division.
22. OGD will issue an AP letter prior to the implementation of the Risk Management Program. However, OGD will not permit marketing of this drug product until after the implementation of the approved RPM.

Date of Review: 2/12/04

Date of Submission: July 2, 2003 & 2/5/04

Primary Reviewer: Chan Park

Date: 2/12/04

Team Leader: Lillie Golson

Date: 2/18/04

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76168AP#2.LABELING.doc
Review

(NOT FINAL, CITIZEN'S PETITION NEEDS TO BE RESOLVED)
(TENTATIVE APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-168 Date of Submission: June 25, 2002

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

CONTAINER LABELS -100s

Satisfactory in **draft** as of 6/25/02 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in **draft** as of 6/25/02 submission

PATIENT PACKAGE INSERT LABELING:

Satisfactory in **draft** as of 6/25/02 submission

REVISIONS NEEDED POST-APPROVAL:

None

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No (Not sure yet)

What is the RLD on the 356(h) form: Oxycontin®

NDA Number: 20-553

NDA Drug Name: Oxycontin®

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:

July 18, 2001/S-022 (Package insert)

January 15, 2002/S-024 (PPI)

Has this been verified by the MIS system for the NDA?

Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the "extended-release" tablets to describe their product as opposed to "controlled-release" used by the innovator. These two terms can be used interchangeably per USP. However, "extended-release" appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). _____ is _____ and USP preferred name for _____ is Triacetin.

6. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020553	001	4861598	AUG 29,2006	
020553	001	4970075	NOV 13,2007	
020553	001	5266331	FEB 05,2008	
020553	001	5508042	APR 16,2013	
020553	001	5549912	FEB 05,2008	
020553	001	5656295	FEB 05,2008	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. The sponsor has filed Paragraph IV Certification against all these patents.

- 4,861,598 Controlled release bases for pharmaceuticals
- 4,970,075 Controlled release bases for pharmaceuticals
- 5,266,331 Controlled release oxycodone compositions
- 5,508,042 Controlled release oxycodone compositions
- 5,549,912 Controlled release oxycodone compositions
- 5,656,295 Controlled release oxycodone compositions

7. The innovator markets 10, 20, 40, 80 (160 mg is discontinued) strengths whereas the sponsor proposed only 80 mg and 160 mg strengths. The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice. This decision was made at the time of review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg & 160 mg has been carved out.
8. The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B. The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R

tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

let Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

Cec,

according to Dr. McCormick (Division Director of HFD-170).". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

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Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn from the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

of not As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne, Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were insensitive to the concerns and were willing to do their part. The big question -- is that a "safety"

reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). The innovator's labeling for Oxycontin still retains all information on 160 mg strength. Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**

11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25oC (60-77oF); brief excursions permitted between 15oC (59oF) and 30oC (86oF).

ANDA: CRT

12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s
ANDA – 100s for both strengths

14. The sponsor will use the _____, manufactured by _____ to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.2, P.3951(80 mg) and B.3.10, p.3659.

16. SCORING – Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC, — cap) with Liner (p.3893, B .1.2 & p.3627, B.3.10 (160 mg))

18. RLD employs a specific delivery form of "_____ tablet. ANDA proposes _____ tablets. The sponsor did not include any specific information associated with the "_____ tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: July 22, 2002

Date of Submission: June 25, 2002

Primary Reviewer: Chan Park

Date: 7/31/02

Acting Team Leader: Lillie Golson

Date: 7/31/02

160 mg strength. We also refer you to the third paragraph of the "Pharmacokinetics and Metabolism" subsection.

iii. Table 1 - Multiple Dose

10 mg oxycodone hydrochloride extended-release tablets q12h [add "extended-release"]

iv. Include Table 2 as found in the innovator's labeling. Please refer to the comment d(ii) above.

e. DRUG ABUSE AND ADDICTION (Head Injury) - Revise to read:

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

f. ADVERSE REACTIONS - Table 3:

Add "Tablets" to read "...Extended-Release Tablets". [2 instances]

g. HOW SUPPLIED

i. We encourage the inclusion of the name and place of business and the revision date.

ii. See GENERAL comment above.

4. PATIENT INFORMATION LEAFLET

a. Who Should Not ... tablets if - 5th bullet:

Include a disclaimer for Tylex, Tylenol with Codeine, and Vicodin" at the end of the labeling.

b. We encourage the inclusion of the storage temperature statement.

c. Please describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets you will supply for each container of 100 tablets and how these leaflets will be supplied.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength. **Then, the sponsor withdrew the proposal for the 160 mg strength in the amendment of May 5, 2003.** See FTR 8 & 10 below.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **consistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 3581, B.1.2 (80 mg) & p.3374, B.3.10 (160 mg). ~~Triacetin~~ and USP preferred name for ~~Triacetin~~ is Triacetin.
6. Patent Data

App No	Prod No	Patent No	Patent Expiration	Use Code
020553	004	4861598	AUG 29,2006	
020553	004	4970075	AUG 29,2006	
020553	004	5266331	OCT 26,2007	
020553	004	5508042	APR 16,2013	U-443
020553	004	5549912	OCT 26,2007	
020553	004	5656295	OCT 26,2007	U-443

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

4,861,598 Controlled release bases for pharmaceuticals
4,970,075 Controlled release bases for pharmaceuticals
5,266,331 Controlled release oxycodone compositions
5,508,042 Controlled release oxycodone compositions
5,549,912 Controlled release oxycodone compositions
5,656,295 Controlled release oxycodone compositions

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75-923 (Endo). However, any other specific information associated with other strengths than 80 mg has been carved out.

8. **The innovator's 160 mg is now discontinued and placed in the D/C section of the O.B.** The sponsor filed a Citizen Petition on September 18, 2001 to find out whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy. The following is the e-mail correspondences in this regard (1/28/02).

Question to Cecilia:

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld for the reasons of safety or efficacy).

Answer from Bob:

Cecelia-

It was an attempt on their part to appear to be dealing with the severe abuse and misuse problem that is occurring with Oxycontin. So it is technically a safety reason. However, it is not clear that the highest dose is the most abused; and it certainly doesn't seem to be the most misused. We have been dealing with this mess nearly every day for a few months now. Let me know if you need any more specific information.

We are having an advisory committee meeting to discuss this and other opiate-related issues on June 14th and 15th and hope you can attend. Please let others in OGD who might be interested in attending this meeting know as well.

9. The following is another e-mail sent to Cecelia Praise on 6/3/02.

Cec,

The following is the e-mail I sent to you on 1/28/02. Have we responded to the sponsor yet? Please be reminded that I was told from HFD-170 (Dr. McCormick) that "The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170)". However, it is found in the D/C section of the Orange Book. I am confused. We are in the process of approving 160 mg Oxycodone tablets from Endo. I guess there is no problem approving the 160 mg strength from Teva as well. Thanks,

Teva filed a citizen's petition for on September 18, 2001 requesting the determination of discontinuation of the RLD 160 mg product. Do we have a response to this petition yet? Please let me know. thanks, (The sponsor wants to know whether Oxycontin E-R tablets, 160 mg was withdrawn voluntarily or withheld from the reasons of safety or efficacy).

Answer from Don Hare to the above e-mail on 6/3/02.

Once the RLD has been moved to the Discontinued Section of the Orange Book, whether it has been officially withdrawn or not, OGD is not permitted to approve an ANDA for this drug product until the determination as to why the drug product was withdrawn from the market and its finding published in the FR Notice. I will check with Dave Read's shop to determine the status of Teva's Petition. Don

Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne,

Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question -- is that a "safety" reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

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11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25°C (60-77°F); brief excursions permitted between 15°C (59°F) and 30°C (86°F).

ANDA: Container - Store at controlled room temperature, between 15° and 30°C (59° and 86°F) [see USP].

Insert Labeling - Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). See GENERAL comment above.

12. DISPENSING STATEMENT

RLD - Dispense in tight, light-resistant container.

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

13. PACKAGING CONFIGURATIONS

RLD: 100s and unit-dose of 25s

ANDA - 100s

14. The sponsor will use the _____, manufactured by _____, to meet the requirement of 21 CFR 1302.06.

15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.2, P.3951(80 mg).

16. SCORING - Both RLD and ANDA unscored.

17. CONTAINER/CLOSURE

Container - HDPE

Closure - 100s (CRC, — cap) with Liner (p.3893, B.1.2)

18. RLD employs a specific delivery form of "_____" tablet. ANDA proposes _____ tablets. The sponsor did not include any specific information associated with the "_____" tablet.

19. Teva is the manufacturer of this drug product.

Date of Review: May 29, 2003

Date of Submission: June 25, 2002 and May 5, 2003

Primary Reviewer: Chan Park

Date: 5/30/03

Team Leader: Lillie Golson

Date: 5/30/03

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76168NA5.LABELING.doc
Review

**APPEARS THIS WAY
ON ORIGINAL**

Superseded by the AP summary prepared on 8/12/04
**(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-168

Date of Submission: July 2, 2003

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS - 100s

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 2)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 3, Rev. 6/03)

PATIENT PACKAGE INSERT LABELING

Satisfactory in FPL as of 7/2/03 submission (vol. 6.1, attachment 4, Rev. 6/03)

REVISIONS NEEDED POST-APPROVAL - INSERT (Adverse Reactions) - Table 3:

Add "Tablets" to the title of second column to read "Immediate-Release Tablets".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: OxyContin® controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.

NDA Number: 20-553

NDA Drug Name: OxyCotin® tablets

NDA Firm: Purdue Pharma L.P.

Date of Approval of NDA Insert and supplement #:
S-022 and S-024/July 18, 2001 & January 15, 2002

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparisons

Other Comments:

The sponsor withdrew the proposal for the 160 mg strength.

FOR THE RECORD:

1. MODEL LABELING – OxyContin controlled-release tablets (20-553/S-022 and S-024). The insert labeling was last approved on July 18, 2001. The patient information leaflet (S-024) was approved January 15, 2002.
2. The sponsor has submitted an amendment on July 25, 2001 adding the 160 mg strength. **Then, the sponsor withdrew the proposal for the 160 mg strength in the amendment of May 5, 2003.** See FTR 8 & 10 below.
3. It is NOT a subject of a USP monograph.
4. The sponsor used the “extended-release” tablets to describe their product as opposed to “controlled-release” used by the innovator. These two terms can be used interchangeably per USP. However, “extended-release” appears to be an official description of release formulation other than immediate-release form. We will not ask the sponsor to revise this term to be same as the innovator.
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6. Patent Data

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020553	004	5508042	APR 16,2013	U-443
020553	004	5549912	OCT 26,2007	
020553	004	5656295	OCT 26,2007	U-443

U-443 - Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's patent and exclusivity statements are accurate. **The sponsor has filed Paragraph IV Certification against all these patents.**

- 4,861,598 Controlled release bases for pharmaceuticals
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The 80 mg and 160 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. "Dose proportionality information" (i.e., the comparison between different strengths tablets) under "CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism" has been retained including all tables per team leader's advice in the past. This decision was made at the time or review of ANDA 75-923 (Endo). However, any other specific information associated with other strengths than 80 mg has been carved out.

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Answer from Bob:

Cecelia-

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Answer from Dave Read to Don Hare on 6/3/02

Don-

I discussed this with Wayne last week, and I regret to report that the situation is a little complicated.

As you know, there are 10, 20, 40, 80, and 160 mg tablets of OxyContin. According to Wayne, Purdue Frederick dropped the 160 in response to the well-publicized concerns about the abuse of OxyContin (the 160s apparently had the biggest street value), that PF did this to show they were not insensitive to the concerns and were willing to do their part. The big question – is that a "safety" reason for purposes of 314.161? As far as I know, that question has not been answered yet.

Dave

10. The innovator does not market the 160 mg strength anymore, but the innovator has NOT withdrawn this strength according to Dr. McCormick (Division Director of HFD-170). **The innovator's labeling for Oxycontin still retains all information on 160 mg strength.** Therefore, it appears safe to assume that there is no specific safety problem related to the 160 mg tablets. In addition, the labeling indicates that two of 80 mg tablets are equivalent to one 160 mg tablet. We are in the process of approving 160 mg Oxycodone tablets from Endo (ANDA 75-923). **However, it now appears that we can't approve the 160 mg strength until we get a response to Teva's CP on 160 mg Oxycontin tablets. We will not request final printed labeling until we are able to provide an adequate response to Teva's petition.**
11. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at controlled room temperature 20-25°C (60-77°F); brief excursions permitted between 15°C (59°F) and 30°C (86°F).

ANDA: Container - Store at controlled room temperature, between 15° and 30°C (59° and 86°F) [see USP].

Insert Labeling - Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP). See GENERAL comment above.
12. DISPENSING STATEMENT

RLD – Dispense in tight, light-resistant container.

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

RLD: 100s and unit-dose of 25s
ANDA – 100s
14. The sponsor will use the , manufactured by to meet the requirement of 21 CFR 1302.06.
15. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.2, P.3951(80 mg).
16. SCORING – Both RLD and ANDA unscored.
17. CONTAINER/CLOSURE

Container – HDPE

Closure – 100s (CRC ← cap) with Liner (p.3893, B .1.2)
18. RLD employs a specific delivery form of tablet. ANDA proposes tablets. The sponsor did not include any specific information associated with the "" tablet.
19. Teva is the manufacturer of this drug product.

20. The sponsor proposed one PPI per a bottle of 100 tablets. I called the firm and spoke with Mr. Philip Erickson on this proposal on August 8, 2003. He stated that their proposal is the same as the innovator's.

Date of Review: August 8, 2003

Date of Submission: July 2, 2003

Primary Reviewer: Chan Park

Date:

8/12/03

Team Leader: Lillie Golson

Date:

8/12/03

cc:

ANDA: 76-168
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76168AP.LABELING.doc
Review

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ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 76-168
3. NAME AND ADDRESS OF APPLICANT
Teva Pharmaceuticals USA
Attention: Phillip Erickson R.Ph.
1090 Horsham Road
P.O. Box 1090
North Wales PA 19454
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Oxycontin. The NDA holder is
Purdue Pharma L.P.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone Hydrochloride
8. SUPPLEMENT PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Orig. Submission May 8, 2001
New Correspondence July 3, 2001
Gratuitous Amendment
for New Strength July 25, 2001
10. PHARMACOLOGICAL CATEGORY
Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Extended release tablet
14. POTENCIES
80 mg
15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-One-
hydrochloride
16. RECORDS AND REPORTS
N/A
17. COMMENTS
FIRST GENERIC.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable; Major

19. REVIEWER:

A.Langowski

DATE COMPLETED:

09/04/01

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ON ORIGINAL**

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12

Page(s) of trade

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commercial

information

1. CHEMISTRY REVIEW NO. 2
2. ANDA 76-168
3. NAME AND ADDRESS OF APPLICANT
Teva Pharmaceuticals USA
Attention: Phillip Erickson R.Ph.
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Oxycontin. The NDA holder is
Purdue Pharma L.P.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone Hydrochloride
8. SUPPLEMENT PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Orig. Submission May 8, 2001
New Correspondence July 3, 2001
Gratuitous Amendment
for New Strength July 25, 2001
Amendment Jan 11, 2002
10. PHARMACOLOGICAL CATEGORY
Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Extended release tablet
14. POTENCIES
80 mg and 160 mg
15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-One-
hydrochloride
16. RECORDS AND REPORTS
N/A
17. COMMENTS
FIRST GENERIC.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable; pending Bio.

19. REVIEWER: DATE COMPLETED:
A.Langowski 02/13/02

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Page(s) of trade

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1. CHEMISTRY REVIEW NO. 3
2. ANDA 76-168
3. NAME AND ADDRESS OF APPLICANT
Teva Pharmaceuticals USA
Attention: Phillip Erickson R.Ph.
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Oxycontin. The NDA holder is
Purdue Pharma L.P.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone Hydrochloride
8. SUPPLEMENT PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Orig. Submission	May 08, 2001
New Correspondence	Jul 03, 2001
Gratuitous Amendment for New Strength	Jul 25, 2001
Amendment	Jan 11, 2002
Amendment	May 07, 2002
Amendment	Jun 25, 2002
Amendment	Dec 04, 2002
10. PHARMACOLOGICAL CATEGORY
Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Extended release tablet
14. POTENCIES
80 mg and 160 mg
15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-One-
hydrochloride
16. RECORDS AND REPORTS
N/A

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Page(s) of trade

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1. CHEMISTRY REVIEW NO. 4
2. ANDA 76-168
3. NAME AND ADDRESS OF APPLICANT
Teva Pharmaceuticals USA
Attention: Phillip Erickson R.Ph.
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Oxycontin. The NDA holder is
Purdue Pharma L.P.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone Hydrochloride
8. SUPPLEMENT PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Orig. Submission	May 08, 2001
New Correspondence	Jul 03, 2001
Gratuitous Amendment for New Strength	Jul 25, 2001
Amendment	Jan 11, 2002
Amendment	May 07, 2002
Amendment	Jun 25, 2002
Amendment	Dec 04, 2002
Amendment	May 05, 2003
Amendment	July 2, 2003
10. PHARMACOLOGICAL CATEGORY
Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Extended release tablet
14. POTENCIES
80 mg
15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-One-
hydrochloride

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1. CHEMISTRY REVIEW NO. 5
2. ANDA 76-168
3. NAME AND ADDRESS OF APPLICANT
Teva Pharmaceuticals USA
Attention: Phillip Erickson R.Ph.
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Oxycontin. The NDA holder is
Purdue Pharma L.P.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Oxycodone Hydrochloride
8. SUPPLEMENT PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Orig. Submission	May 08, 2001
New Correspondence	Jul 03, 2001
Gratuitous Amendment for New Strength	Jul 25, 2001
Amendment	Jan 11, 2002
Amendment	May 07, 2002
Amendment	Jun 25, 2002
Amendment	Dec 04, 2002
Amendment	May 05, 2003
Amendment	July 2, 2003
Amendment (minor)	Dec 19, 2003
Amendment (tele)	Jan 16, 2004
10. PHARMACOLOGICAL CATEGORY
Analgesic
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Extended release tablet
14. POTENCIES
80 mg

(u) 3-25-04

14

15. CHEMICAL NAME AND STRUCTURE
4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one-
hydrochloride
16. RECORDS AND REPORTS
N/A
17. COMMENTS
~~FIRST GENERIC~~ *uv*
18. CONCLUSIONS AND RECOMMENDATIONS
Approvable
19. REVIEWER: A.Langowski DATE COMPLETED: 01/08/04; 01/20/04

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

**BIOEQUIVALENCE
REVIEW(S)**

Oxycodone Hydrochloride ER Tablets
80 mg
ANDA 76-168
Reviewer: Z.Z. Wahba
V:\firmsnz\TEVA\let&rev\76168S.501

Teva Pharmaceuticals USA
North Wales, PA
Submission Date: 05/08/01

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests
(Electronic Submission)

Introduction

Indication: the management of moderate to severe pain.

Type of Submission: Original

RLD: Purdue Pharma LP's OxyContin® 80 mg Tablets.

Background

Oxycodone hydrochloride is a strong opioid analgesic. It is well absorbed with a bioavailability of 60% to 87%. Upon repeated dosing in normal volunteers, steady-state levels were achieved within 24 - 36 hours. Dose proportionality has been established for the 10-mg, 20-mg and 40-mg tablet strengths for both peak plasma levels (Cmax) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone. The most common adverse experiences reported in controlled clinical trials included: constipation, nausea, somnolence, dizziness, vomiting, headache, dry mouth, asthenia, and sweating (PDR 2000). Oxycodone is currently available as OxyContin® in 10-mg, 20-mg, 40-mg and 80-mg controlled-release tablets marketed by Purdue Pharma LP.

BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

Protocol No.: 315-31,

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: _____

Medical Director: _____

Clinical Study Dates: 02/21/01 to 03/03/01

Analytical Facility _____

Principal Investigator: _____

Analytical Study Dates: 03/09/01 to 03/21/01

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Oxycodone HCl ER Tabs	OxyContin®

Manufacturer:	TEVA Pharmaceuticals USA	The PF Laboratories, Inc.
Manufacture Date:	1/16/01	N/A
Expiration Date:	N/A	8/04
Full Batch Size:	units	N/A
Batch/Lot Number:	1313-157	7J3N1
Potency:	98.2%	96.5%
Content Uniformity:	100.2%	98.7%
Strength:	80 mg	80 mg
Dosage Form:	tablet	tablet
Dose Administered:	80 mg	80 mg
Study Condition:	fasting	fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment	N
		Design:	
No. of Periods:	2	Balanced:	Y
No. of Treatments:	2	Washout Period:	7 Days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent	Y
		Obtained:	
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	30
Route of Administration:	Oral	No. of Subjects	29
		Completing:	
Dosing Interval:	hr	No. of Subjects Plasma	29
		Analyzed:	
Number of Doses:	N/A	No. of Dropouts:	1
Loading Dose:	mg	Sex(es) Included:	male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	0

Dietary Restrictions: The use of foods or beverages containing alcohol or caffeine/xanthine was prohibited for 48 hr prior to and during each period of confinement. The use of foods or beverages containing grapefruit or grapefruit juice was prohibited for 72 hr prior to and during each confinement.

Activity Restrictions: Subjects were not permitted to lie down for the first 4 hours following drug administration.

Drug Restrictions: No prescription medications within 14 days prior to or during the study. No OTC medications within 7 days prior to or during each study period. Exceptions may be allowed at the discretion of the Sponsor providing it had no impact on the study.

Blood Sampling: Blood samples (10 mL EDTA) were collected during each study period at Hour 0 (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours postdose.

Demographic Data	<ul style="list-style-type: none"> • 30 subjects enrolled. • 29 subjects completed. • Gender: 30 males • Race: 25 Caucasians, 2 Blacks, 1 American Indian, 1 Asian, and 1 Hispanic. • Age: Average 36 years (20-55 years) Zero subjects < 18 years 23 subjects between 18-40 years 7 subject between 41-64 years zero subjects between 65-75 years zero subjects between > 75 years • Height (cm): Average 177 (163-192) • Weight (kg): 77.9 (59.9-95.5)
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Dropouts:

SUBJECT NO.: 19
REASON: Dropped by Investigator prior to dosing in Period 2 due to ongoing headache and nausea
PERIOD: 2
REPLACEMENT: N

Note: Each subject received a single oral dose of the opiate antagonist ReVia® (naltrexone) tablet (50 mg dose) taken with 240 mL of water at 15 hours and 3 hours prior to each dose of oxycodone HCl.

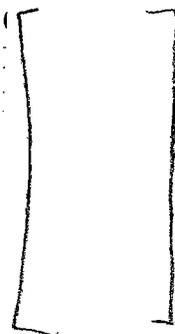
Adverse Events:

Eight subjects experienced a total of nineteen (19) adverse events during this study. All medical events were mild. The adverse events were judged as 14 drug-related, 1 probably drug-related, and 4 unrelated drug-related (page 289, volume C1.2).

Analytical Method (Not to be Released Under FOI)

Pre-Study Assay Validation:

ANALYTE:
ASSAY METHOD:
MATRIX:
INTERNAL STANDARD:
SENSITIVITY:
STANDARD CURVE
HIGHEST CONC.:
STANDARD CURVE
LOWEST CONC.:
SPECIFICITY:



PRE-STUDY ASSAY VALIDATION

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	[]
Intra Day Precision (%CV)		
Intra Day Accuracy (% of change)		
Inter Day Precision (%CV)		
Inter Day Accuracy (% of change)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)]	
Recovery (%)		
Stability		
Specificity	[]

DURING STUDY ASSAY VALIDATION FOR FASTING STUDY

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	[]
Inter Day Precision (%CV)		
Inter Day Accuracy (% of change)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Pharmacokinetic:

The plasma concentrations and pharmacokinetic parameters of oxycodone under fasting conditions were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for oxycodone are summarized in the tables below:

Table #1
Mean Plasma Concentrations (ng/mL)
of Oxycodone Under Fasting Conditions (n=29)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	9.68	5.34	11.45	7.01	0.85
1	31.02	9.45	38.62	15.37	0.80
2	48.56	12.71	55.07	15.64	0.88
3	59.11	15.60	58.86	16.08	1.00
4	61.38	14.89	57.53	14.85	1.07
5	65.86	15.48	58.75	14.58	1.12
6	59.44	14.12	52.24	12.73	1.14
7	55.34	13.09	47.85	12.48	1.16
8	50.54	13.05	43.23	12.42	1.17
10	42.11	12.64	34.38	10.21	1.22
12	33.86	11.58	28.63	7.78	1.18
16	20.01	7.23	20.22	5.77	0.99
24	7.66	3.84	10.85	4.18	0.71
36	1.31	1.06	2.07	1.31	0.63
48	0.24	0.28	0.44	0.41	0.55

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #2
Summary of Pharmacokinetics Parameters (Oxycodone)
Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	855.44	231.62	846.01	210.00	1.01
AUCT	851.70	231.02	841.03	208.88	1.01
C _{MAX}	68.47	16.25	62.48	14.90	1.10
KE	0.15	0.02	0.14	0.02	1.09
*LAUCI	825.10	0.28	819.18	0.27	1.01
*LAUCT	821.43	0.28	814.32	0.27	1.01
*LC _{MAX}	66.68	0.23	60.71	0.25	1.10
THALF	4.83	0.86	5.29	1.08	0.91
T _{MAX}	4.66	0.82	3.37	1.33	1.38

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Table #3
LSMeans and 90% Confidence Intervals
(Oxycodone)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	832.06	819.18	1.02	95.69	107.82
LAUCT	828.33	814.32	1.02	95.84	107.96
LCMAX	66.87	60.71	1.10	103.90	116.78

LSMEAN1=LS mean test

Low CI 12=Lower C.I. for T/R

UNIT: AUC=NG HR/ML

LSMEAN2=LS mean ref.

UPP CI 12=Upper C.I. for T/R

CMAx=NG/ML

Comment on the fasting study (Oxycodone):

Under fasting conditions, the mean plasma oxycodone levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).

BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS

Protocol No.: 315-30

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: _____

Medical Director: _____

Clinical Study Dates: 02/17/01 to 02/27/01

Analytical Facility _____

Principal Investigator: _____

Analytical Study Dates: 03/06/01 to 03/16/01

TREATMENT INFORMATION

Treatment ID:

A

B

Test or Reference:

T

R

Product Name:

Oxycodone HCl ER Tabs

OxyContin

Manufacturer:

TEVA Pharmaceuticals USA

The PF Laboratories, Inc.

Manufacture Date:

1/16/01

N/A

Expiration Date:

N/A

8/04

Batch/Lot Number:

1313-157

7J3N1

Strength:

80 mg

80 mg

Dosage Form:

Tablet

Tablet

Dose Administered:

80 mg

80 mg

Study Condition:

Fed

Fed

Length of Fasting:

Overnight

Overnight

Standardized Breakfast:

Y

Y

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment	N
No. of Periods:	2	Design:	
No. of Treatments:	2	Balanced:	Y
		Washout Period:	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent	Y
		Obtained:	
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	30
Route of Administration:	Oral	No. of Subjects	30
		Completing:	
Dosing Interval:	hr	No. of Subjects Plasma	30
		Analyzed:	
Number of Doses:	N/A	No. of Dropouts:	0
Loading Dose:	mg	Sex(es) Included:	male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	0

Dietary Restrictions: The use of foods or beverages containing alcohol or caffeine/xanthine was prohibited 48 hrs & the use of foods or beverages containing grapefruit or grapefruit juice was prohibited for 72 hrs prior to and during each period of confinement.

Activity Restrictions: The subjects were not to engage in strenuous exercise during the confinement period and subjects were not permitted to lie down for the first 4 hours following drug administration.

Drug Restrictions: No prescription medication within 14 days prior to or during the study. No OTC medication within 7 days prior to or during the study - exceptions were allowed at the discretion of the sponsor providing it did not impact the study.

Blood Sampling: Blood samples (10 mL EDTA) were collected during each study period at Hour 0 (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours postdose.

Demographic Data	<ul style="list-style-type: none"> • 30 subjects enrolled. • 30 subjects completed. • Gender: 30 males • Race: 27 Caucasians, 1 Black, 1 White Non-Caucasian, and 1 Hispanic. • Age: Average 37 years (24-53 years) Zero subjects < 18 years 19 subjects between 18-40 years 11 subject between 41-64 years zero subjects between 65-75 years
------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

	zero subjects between > 75 years • Height (cm): Average 176 (165-187) • Weight (kg): 78.9 (67.9-93.4)
--	-------------------------------------------------------------------------------------------------------------

Dropouts:
 No Dropouts Reported

Note: Each subject received a single oral dose of the opiate antagonist ReVia® (naltrexone) tablet (50 mg dose) taken with 240 mL of water at 15 hours and 3 hours prior to each dose of oxycodone HCl.

Adverse Events:
 Nine subjects experienced a total of sixteen (16) adverse events during this study. All medical events were mild to moderate. The adverse events were judged as 7 drug-related, 1 probably drug-related, 1 possible drug-related, 1 unlikely drug-related, and 6 unrelated drug-related (page 1992, volume C1.6).

Assay Methodology: (NOT TO BE RELEASED UNDER FOI)

DURING STUDY ASSAY VALIDATION FOR FASTING STUDY

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	{	}
Inter Day Precision (%CV)		
Inter Day Accuracy (% of change)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Pharmacokinetic:

The plasma concentrations and pharmacokinetic parameters of oxycodone under non-fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

The plasma concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

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 ON ORIGINAL**

Table #4
Mean Plasma Concentrations (ng/mL)
of Oxycodone Under non-fasting Conditions (N=30)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	4.18	4.04	5.40	6.75	0.77
1	22.62	14.92	25.17	18.20	0.90
2	56.52	19.15	56.01	18.87	1.01
3	77.07	19.92	72.14	16.55	1.07
4	80.75	18.27	73.50	13.68	1.10
5	87.20	19.59	73.61	15.41	1.18
6	77.22	17.49	65.29	14.96	1.18
7	71.70	19.44	60.08	15.38	1.19
8	62.27	16.27	55.07	15.14	1.13
10	47.72	16.22	41.71	13.14	1.14
12	34.90	11.45	33.81	12.03	1.03
16	19.76	8.51	22.74	8.26	0.87
24	7.00	3.95	10.59	4.42	0.66
36	1.11	0.88	1.91	1.35	0.58
48	0.25	0.29	0.45	0.44	0.56

1=Test-NonFast

2=Ref.-NonFast

UNIT: PLASMA LEVEL=NG/ML

TIME=HRS

Table #5
Summary of Pharmacokinetics Parameters (Oxycodone)
Under Fasting and Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	968.69	243.98	961.93	231.89	1.01
AUCT	965.12	243.45	957.17	230.18	1.01
C _{MAX}	91.12	18.27	80.85	13.37	1.13
KE	0.15	0.03	0.13	0.02	1.10
*LAUCI	938.59	0.26	934.32	0.25	1.00
*LAUCT	935.01	0.26	929.80	0.25	1.01
*LC _{MAX}	89.21	0.22	79.70	0.18	1.12
THALF	4.80	0.78	5.29	0.98	0.91
T _{MAX}	4.57	1.01	3.53	1.17	1.29

1=Test-NonFast

2=Ref.-NonFast

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study

Under non-fasting conditions, the mean plasma oxycodone levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The T/R geometric mean ratios (RMEAN1/2) for AUC_t, AUC_i, and C_{max} were within the acceptable range of 0.8-1.25% (Table #5).

Redacted _____

*P210
Formulation*

Page(s) of trade

secret and /or

confidential

commercial

information

Dissolution(Not to be released under FOI)

IN VITRO DISSOLUTION TESTING						
Drug: Oxycodone Hydrochloride Extended-Release Tablets						
Dose Strength: 80 mg						
Firm: TEVA Pharmaceuticals USA						
Submission Date: May 8, 2001						
File Name: Oxycodone Hydrochloride Extended-Release Tablets, 80 mg						
I. Conditions for Dissolution/Release Testing:						
USP 23 Apparatus: 1			Medium: Intestinal Fluid, Simulated, TS (no enzyme)			
RPM: 100			Volume: 900 mL			
No. Units Tested: 12			Assay Method: —			
Reference Drug: OxyContin® (Oxycodone Hydrochloride Controlled-Release Tablets), 80 mg						
II. Results of <i>In Vitro</i> Dissolution/Release Testing:						
Sampling Times (min)	Test Product: Lot No.: 1313-157 Strength: 80 mg			Reference Product: Oxycontin® Lot No.: 7J3N1 Strength: 80 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
30	19.2	[]	5.1	27.5	[]	1.7
60	29.6		5.2	37.7		1.3
120	45.2		4.8	50.0		1.5
240	66.7		4.4	64.7		1.5
480	89.4		3.4	81.8		1.2
720	98.0		3.1	91.7		1.0
Content Uniformity (10 Units); Potency Assay:						
Test Product Lot = Content Uniformity Mean = 100.2%, RSD = 3.1%; Assay = —						
Reference Product Lot = Content Uniformity Mean = 98.7%, RSD = 0.5%; Assay = —						

IN VITRO DISSOLUTION TESTING						
Drug: Oxycodone Hydrochloride Extended-Release Tablets						
Dose Strength: 80 mg						
Firm: TEVA Pharmaceuticals USA						
Submission Date: May 8, 2001						
I. Conditions for Dissolution/Release Testing:						
USP 23 Apparatus: 1			Medium: Gastric Fluid (no enzyme)			
RPM: 100			Volume: 900 mL			
No. Units Tested: 12			Assay Method: —			
Reference Drug: OxyContin® (Oxycodone Hydrochloride Controlled-Release Tablets), 80 mg						
II. Results of <i>In Vitro</i> Dissolution/Release Testing:						
Sampling Times (min)	Test Product: Lot No.: 1313-157 Strength: 80 mg			Reference Product: Oxycontin® Lot No.: 7J3N1 Strength: 80 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
30	18.4	[]	5.7	27.9	[]	1.6
60	28.8		6.0	39.1		1.2
120	44.6		6.0	52.9		1.3
240	67.1		5.7	69.7		1.4
480	90.7		4.3	88.4		1.4
720	99.0		4.0	98.4		1.0

IN VITRO DISSOLUTION TESTING						
Drug: Oxycodone Hydrochloride Extended-Release Tablets						
Dose Strength: 80 mg						
Firm: TEVA Pharmaceuticals USA						
Submission Date: May 8, 2001						
I. Conditions for Dissolution/Release Testing:						
USP 23 Apparatus: 1			Medium: Phosphate Buffer pH 3.0			
RPM: 100			Volume: 900 mL			
No. Units Tested: 12			Assay Method: _____			
Reference Drug: Oxycontin [®] (Oxycodone Hydrochloride Controlled-Release Tablets), 80 mg						
II. Results of <i>In Vitro</i> Dissolution/Release Testing:						
Sampling Times (min)	Test Product: Lot No.: 1313-157 Strength: 80 mg			Reference Product: Oxycontin [®] Lot No.: 7J3N1 Strength: 80 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
30	19.1	[]	7.5	29.2	[]	1.4
60	29.9		7.0	40.5		1.4
120	46.3		6.5	54.4		1.2
240	68.2		5.0	71.1		1.1
480	90.5		2.9	89.4		1.0
720	97.6		2.8	98.8		0.9

IN VITRO DISSOLUTION TESTING						
Drug: Oxycodone Hydrochloride Extended-Release Tablets						
Dose Strength: 80 mg						
Firm: TEVA Pharmaceuticals USA						
Submission Date: May 8, 2001						
I. Conditions for Dissolution/Release Testing:						
USP 23 Apparatus: 1			Medium: Acetate Buffer pH 5.0			
RPM: 100			Volume: 900 mL			
No. Units Tested: 12			Assay Method: _____			
Reference Drug: OxyContin [®] (Oxycodone Hydrochloride Controlled-Release Tablets), 80 mg						
II. Results of <i>In Vitro</i> Dissolution/Release Testing:						
Sampling Times (min)	Test Product: Lot No.: 1313-157 Strength: 80 mg			Reference Product: Oxycontin [®] Lot No.: 7J3N1 Strength: 80 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
30	19.2	[]	4.4	30.4	[]	1.7
60	29.2		4.6	41.9		1.3
120	44.1		4.5	56.1		1.1
240	65.1		4.1	73.0		1.1
480	88.0		2.8	91.3		1.1
720	97.0		2.3	100.3		1.0

IN VITRO DISSOLUTION TESTING						
Drug: Oxycodone Hydrochloride Extended-Release Tablets						
Dose Strength: 80 mg						
Firm: TEVA Pharmaceuticals USA						
Submission Date: May 8, 2001						
I. Conditions for Dissolution/Release Testing:						
USP 23 Apparatus: 1			Medium: Water			
RPM: 100			Volume: 900 mL			
No. Units Tested: 12			Assay Method: —			
Reference Drug: Oxycontin® (Oxycodone Hydrochloride Controlled-Release Tablets), 80 mg						
II. Results of <i>In Vitro</i> Dissolution/Release Testing:						
Sampling Times (min)	Test Product: Lot No.: 1313-157 Strength: 80 mg			Reference Product: Oxycontin® Lot No.: 7J3N1 Strength: 80 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
30	19.2	[]	4.9	27.1	[]	2.0
60	29.8		5.1	37.6		1.2
120	45.9		4.8	50.2		1.0
240	67.4		3.8	65.4		1.2
480	87.2		3.1	82.0		1.0
720	91.4		3.2	90.8		0.9

Comments on the Dissolution:

- The firm proposes dissolution testing in 900 mL of Simulated Intestinal Fluid without enzyme using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following tentative specifications:

Time (minutes)	Mean (% of claim)
60	—
240	—
480	NLT —

- DBE proposes a different method, based on in-house information (ANDA 65-923), and discussion with Dr. Nhan Tran, the DBE liason to the USP. For the sake of consistency, the following method using 0.1N HCl and specifications may be suggested to the firm. Dr. Tran pointed out that the USP prefers to use simulated gastric fluid without enzyme, which is similar to 0.1N HCl. The firm submitted acceptable dissolution data in simulated gastric fluid without enzyme (see second dissolution data table, above). These data were used to determine the proposed specifications.

Therefore, DBE requests that the dissolution testing may be conducted in 900 mL of 0.1N HCl at 37°C using USP Apparatus I at 100 rpm.

1 hour	—
4 hours	—
12 hours	NLT —

GENERAL COMMENTS:

1. The firm's *in vivo* bioequivalence study conducted by Teva Pharmaceuticals on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg, under nonfasting conditions is acceptable. The T/R geometric mean ratios are within the acceptable range of 0.80-1.25 for AUC(0-t), AUCinf and Cmax.
2. The dissolution testing conducted by the firm on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg, Lot # 1313-157, is acceptable. The dissolution testing method using 900 mL of Simulated Intestinal Fluid without enzyme appears to be adequately discriminating for routine dissolution testing for Oxycodone Hydrochloride Extended Release Tablet, 80 mg.
3. All inactive ingredients in the formulation were found to be within approved safety limits (FDA Inactive Ingredient Guide, January 1996).

DEFICIENCY COMMENT:

The CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified release products. The firm should explain why it conducted a two-way crossover design for its fasting bioequivalence study on Oxycodone Hydrochloride Extended Release Tablet, 80 mg, instead of using a replicate design.

**APPEARS THIS WAY
ON ORIGINAL**

RECOMMENDATIONS:

1. The bioequivalence study under fasting conditions conducted by Teva Pharmaceuticals USA, on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg, lot #1313-157, comparing it to Purdue Pharma's OxyContin® Extended Release Tablet, 80 mg, has been found incomplete for the reason given in the deficiency comment.
2. The dissolution testing conducted by the firm on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg, lot #1313-157, is acceptable.
3. 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 Apparatus I (basket) at 100 rpm. The test product should meet the following tentative specifications:

1 hour ~
4 hours ~
12 hours NLT ~

The firm should be informed of the deficiency comment and recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

B7ND 10/15/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT

(Babunur N. Saif)

Date *10/10/01*

Concur: *Dale P. Conner*

Date: *10/15/2001*

fr Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-168

APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Oxycodone HCl Extended Release Tablet, 80 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified-release products. Please explain why you used a two-way crossover design for your fasting bioequivalence study instead of a replicate design.

Sincerely yours,



fr

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

CC: ANDA #76-168
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer Z. Wahba
HFD-658/ Bio team Leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Z. Wahba *ZW 10/9/01*
HFD-658/ B. Davit *BVD 10/10/01*
HFD-650/ D. Conner *for dup 10/11/2001*

BIOEQUIVALENCY - DEFICIENCY

submission date: May 08, 2001

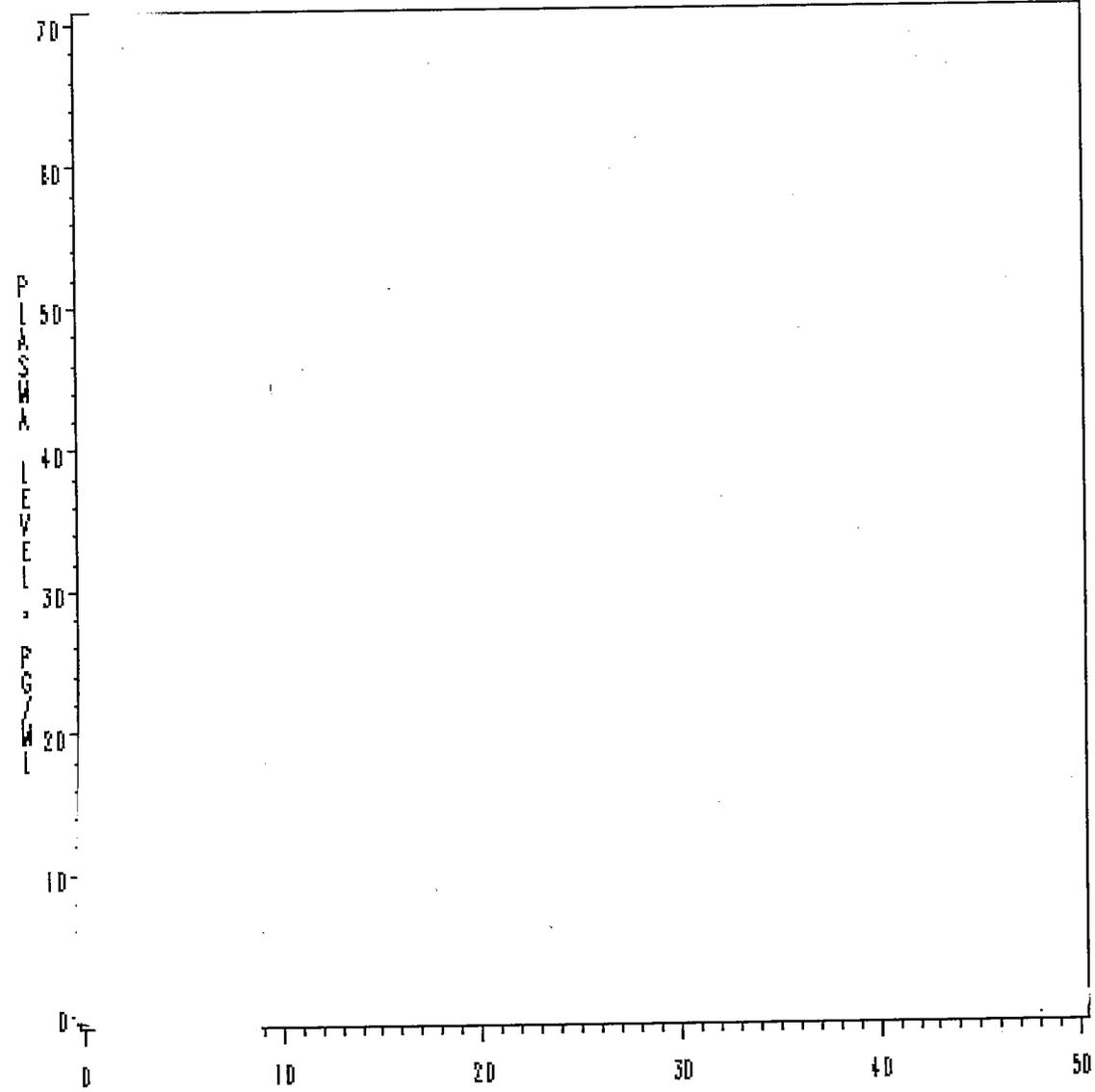
- | | | |
|--------------|--------------------------------------------|--------------------------------|
| <i>Sh</i> 1. | FASTING STUDY (STF)
Clinical Sit: _____ | Strength: 80 mg
Outcome: IC |
| <i>cu</i> 2. | FOOD STUDY (STP)
Clinical Sit: _____ | Strength: 80 mg
Outcome: AC |

Outcome Decisions: IC – Incomplete
Winbio comments: STF – Incomplete
STA– Incomplete

**APPEARS THIS WAY
ON ORIGINAL**

FIG P-1 . PLASMA OXYCODONE LEVELS

OXYCODONE HCL ER TABLETS, 80 MG, ANDA #76-168
UNDER FASTING CONDITIONS
DOSE=1 X BD QD



TRT ***1 BBB 2

1=TEST(TEVA) 2=REF(PURDUE-PHARMA LP)

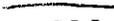
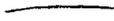
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-168 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Oxycodone HCl Extended Release Tablet, 80 mg, 160 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs: The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme at 37°C using USP Apparatus 1 (basket) at 100 rpm. The test product should meet the following tentative specifications:

1 hour	
4 hours	
12 hours	NLT 

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,



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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-168 SPONSOR : Teva Pharmaceuticals
DRUG AND DOSAGE FORM: Oxycodone Extended-Release Tablets
STRENGTH(S): 80 mg, 160 mg
TYPES OF STUDIES: Single-dose fasting and postprandial studies.
CLINICAL STUDY SITE: _____
ANALYTICAL SITE: _____
STUDY SUMMARY: Acceptable fasting and postprandial studies (for the 80 mg and 160 mg strengths)

DISSOLUTION: The dissolution data for the 80 mg and 160 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: <u>No</u>	Inspection status:	Inspection results:
First Generic <u>No</u> New facility <u>No</u> For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Zakaria Z. Wahba BRANCH: III

INITIAL: ZZW DATE: 3/7/02

TEAM LEADER: Mamata Gokhale, Ph.D BRANCH: III

INITIAL: MSK DATE: 3/7/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DP DATE: 11/4/02

**OXYCODONE HYDROCHLORIDE
EXTENDED-RELEASE TABLETS**

80 mg and 160 mg

ANDA 76-168

Reviewer: Z.Z.Wahba

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Teva Pharmaceuticals USA

North Wales, PA

Submission Date:

07/25/01

01/11/02

Study Amendment on the 80 mg Strength

And

**Review of Two Additional Bioequivalence Studies, Dissolution Data on the 160 mg Strength
(Electronic Submission)**

Background

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Oxycodone Hydrochloride Extended Release Tablet, 80 mg, to Purdue Pharma's OxyContin® Extended Release Tablet, 80 mg. The submission was reviewed and was found incomplete by the Division of Bioequivalence (the review date 10/15/2001) due to deficiency comment.
2. In this submission, the firm has responded to the deficiency comment and included additional information in the current submission.
3. In addition, the firm submitted two bioequivalence studies under fasting and non-fasting conditions, comparing its Oxycodone Hydrochloride Extended Release Tablet, 160 mg, strength to the reference product Purdue Pharma's OxyContin® Extended Release Tablet, 160 mg.
4. The RLD Purdue Pharma's OxyContin® Extended Release Tablet, 160 mg, is on the discontinued drug product list in the 2002 Orange Book.
5. On 09/18/01, the firm submitted a Citizen Petition (CP) for Oxycodone Hydrochloride Extended Release Tablet, 160 mg. The CP is seeking determination whether Purdue Pharma's OxyContin® Extended Release Tablet, 160 mg, was withdrawn from the market for safety or effectiveness reasons.
6. The approval of the 160 mg strength is pending on the approval of the Citizen Petition for the RLD Purdue Pharma's OxyContin® Extended Release Tablet, 160 mg. The Citizen Petition is currently being reviewed.

DEFICIENCY COMMENT

On 10/24/01, the DBE requested the firm to respond to the following comment:

CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design

bioequivalence studies are recommended for modified-release products. Please explain why you used a two-way crossover design for your fasting bioequivalence study instead of a replicate design

RESPONSE TO THE DEFICIENCY COMMENT

To minimize the risk of respiratory depression associated with opioid analgesics (such as oxycodone), the firm conducted the bioequivalence study as two-way crossover design. In this way of design the subjects received two doses of the drug instead of the four doses required by a replicate design study.

Note: Currently, the DBE has dropped its requirements for conducting replicate design bioequivalence studies for modified-release products, as per recommendation from the meeting of the advisory committee for Pharmaceutical Science (11/29/01).

The firm's response to the deficiency comment is acceptable.

BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS (160 mg)

Protocol No.: 315-32

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	_____
Principal Investigator:	_____
Clinical Study Dates:	05/10/01 to 05/27/01
Analytical Facility	_____
Analytical Study Dates:	06/01/01 to 06/12/01

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Oxycodone HCl	OxyContin®
Manufacturer:	TEVA Pharmaceuticals USA	The PF Laboratories, Inc.
Manufacture Date:	04/30/01	N/A
Expiration Date*:	N/A	11/30/03
Batch Size:	_____ units	N/A
Batch/Lot Number:	1404-003	9V51
Potency:	99.6%	101.9%
Content Uniformity:	100.6%	101.4%
Strength:	160 mg	160 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1X160 mg	1X160 mg
Study Condition:	Fasting	fasting
Length of Fasting:	10 hours	10 hours

*The information reported in pages 111 (volume B3.2) and 1773 (volume B3.7).

RANDOMIZATION**DESIGN**

Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	N
No. of Treatments:	2	Washout Period:	7 Days

DOSING**SUBJECTS**

Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	30
Route of Administration:	oral	No. of Subjects Completing:	28

Dietary Restrictions:	The use of foods containing alcohol or caffeine/xanthine was prohibited 48 hr prior to & during each period of confinement. The use of foods or beverages containing grapefruit was prohibited for 72 hr prior to & during each confinement period.
Activity Restrictions:	Subjects were not permitted to lie down for the first 4 hours following drug administration unless necessitated by an adverse event. Subjects were not to engage in strenuous exercise during the confinement period of the study.
Drug Restrictions:	No prescription medication within 14 days period to or during the study. No OTC medication within 7 days prior to or during the study - exceptions were allowed at the discretion of the sponsor providing it did not impact the study.
Blood Sampling:	Blood samples (10 mL EDTA) were collected during each study period at Hour 0 (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours postdose.

Demographic Data*	<ul style="list-style-type: none"> • 30 healthy subjects enrolled. • Gender: 30 males • Race: 25 Caucasians, 3 Hispanic, 2 Blacks • Age: Average 45 years (21-75 years) Zero subjects < 18 years 14 subjects between 18-40 years 11 subject between 41-64 years 5 subjects between 65-75 years zero subjects between > 75 years • Height (in): Average 71.0 (64.5-77.5) • Weight (lb): 178.7 (128.0-211.0)
*Information on pages 172-173, vol. B3.3	

Note: Each subject received a single oral dose of the opiate antagonist ReVia® (naltrexone) tablet (2 X 50 mg dose) taken with 240 mL of water at 15 hours and 3 hours prior to each dose of oxycodone HCl. Naltrexone was administered to block the opioid adverse effects associated with high dose of oxycodon.

Dropouts:

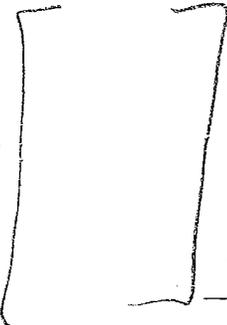
SUBJECT NO.:	1	10
REASON:	Subject vomited after naltrexone admin. and was dropped by the principal investigator.	Subject has a positive cotinine result at Period 2.
PERIOD:	2	2

REPLACEMENT:	N	N
--------------	---	---

Adverse Events:

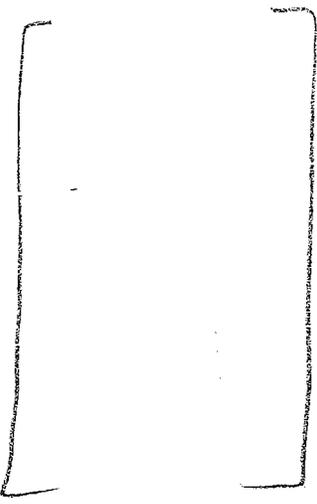
Eight subjects experienced a total of twenty-one (21) adverse events during this study. All medical events were moderate. The adverse events were judged as 9 possibly drug-related, 9 probably drug-related, and 3 unrelated drug-related (page 274, volume B3.3).

Analytical Assay (Not to be Released Under FOI)

ANALYTE:		
ASSAY METHOD:		
MATRIX:		
INTERNAL STANDARD:		
SENSITIVITY:		
STANDARD CURVE HIGHEST CONC.:		
STANDARD CURVE LOWEST CONC.:		
R*2 IS GREATER THAN:		
SPECIFICITY:		

STUDY ASSAY VALIDATION (Not to be released under FOI)

(Note: the assay validation for oxycodone was previously demonstrated in two biostudies for the 80 mg strength)

Parameter	Quality Control Samples
QC or Std. Curve Conc. (ng/mL)	
Intra Day Precision (%CV)	
Intra Day Accuracy (% of change)	
Inter Day Precision (%CV)	
Inter Day Accuracy (% of change)	
Linear Range (ng/mL)	
Sensitivity/LOQ (ng/mL)	
Recovery (%)	
Stability*	

*The information on pages 322-329, volume B3.3.

DURING STUDY ASSAY VALIDATION FOR FASTING STUDY*

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	[]
Inter Day Precision (%CV)		
Inter Day Accuracy (% of change)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

*The information on pages 348-349, volume B3.3.

**There was one anomalous value (one out of 20 QC samples) for the _____, quality control on standard curve OXY_008 which caused the high value of coefficient of variation. The standard curve OXY-008 met the acceptance criteria (page 345, volume B3.3).

Pharmacokinetic:

The plasma concentrations and pharmacokinetic parameters of oxycodone under fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

PK Results:

Mean Plasma Concentrations: Table 1, Figure 1

Pharmacokinetic Parameters: Tables 2 and 3

PK Parameter	90% Confidence Intervals (n=27)	Geometric T/R Ratios (n=27)	Root MSE
LAUC _t	93.56-102.52%	0.98	0.09827255
LAUC _i	93.43-102.95%	0.98	0.10047493
LCMAX	89.87-99.27%	0.94	0.10688170

Comments:

- There were no measurable drug concentrations in the pre-dose samples. There was no observation of a first measurable drug concentration as C_{max}.
- The reviewer recalculated pharmacokinetic parameters. The reported values are in agreement with those obtained by the reviewer.
- The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%.
- Subject #28, vomited approximately 10 hr and 11.5 hrs after dosing (test product), in period 1. According to the CDER Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" (10/2000), subject #28, should be deleted from the statistical analysis. However, if subject #28 is included in the statistical analysis, the outcome decision on the application will remain the same (see Table #4).

Conclusion: The fasting study is acceptable.

BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (160 mg)

Protocol No.: 315-33

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	_____
Principal Investigator:	_____
Clinical Study Dates:	05/11/01 to 05/21/01
Analytical Facility	_____
Analytical Study Dates:	05/25/01 to 06/11/01

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Oxycodone HCl	OxyContin®
Manufacturer:	TEVA Pharmaceuticals USA	The PF Laboratories, Inc.
Manufacture Date:	04/30/01	N/A
Expiration Date:	N/A	11/30/03
Batch Size:	_____ units	N/A
Batch/Lot Number:	1404-003	9V51
Strength:	160 mg	160 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1X160 mg	1X160 mg
Study Condition:	Fed	Fed
Standardized Breakfast:	Y	Y

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	N
No. of Treatments:	2	Washout Period:	7 Days

DOSING

SUBJECTS

Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	30
Route of Administration:	oral	No. of Subjects Completing:	25

Dietary Restrictions:	The use of foods containing alcohol or caffeine/xanthine was prohibited 48 hr prior to & during each period of confinement. The use of foods or beverages containing grapefruit was prohibited for 3 days prior to the study.
Activity Restrictions:	Subjects were not permitted to lie down for the first 4 hours following drug administration unless necessitated by an adverse event. Subjects were not to engage in strenuous exercise during the confinement period of the study.

Drug Restrictions:	No prescription medication within 14 days prior to or during the study. No OTC medication within 7 days prior to or during the study - exceptions were allowed at the discretion of the sponsor providing it did not impact the study.
Blood Sampling:	Blood samples (10 mL EDTA) were collected during each study period at Hour 0 (predose), and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours postdose.

Demographic Data*	<ul style="list-style-type: none"> • 30 healthy subjects enrolled. • Gender: 30 males • Race: 27 Caucasians, 2 Blacks, 1 Asian • Age: Average 27 years (19-57 years) Zero subjects < 18 years 26 subjects between 18-40 years 14 subject between 41-64 years Zero subjects between 65-75 years zero subjects between > 75 years • Height (in): Average 71.5 (65.0-76.0) • Weight (lb): 173.9 (146.0-206.0)
*Information on pages 1782-1783, vol. B3.7	

Note: Each subject received a single oral dose of the opiate antagonist ReVia® (naltrexone) tablet (2 X 50 mg dose) taken with 240 mL of water at 15 hours and 3 hours prior to each dose of oxycodone HCl.

Dropouts:

SUBJECT NO.:	1	17	20
REASON:	Subject was dropped after oxycodone dosing due to adverse events	Subject was dropped prior to oxycodone dosing due to an adverse event	Subject was dropped prior to Period 2 for personal reasons
PERIOD:	1	2	1
REPLACEMENT:	N	N	N

SUBJECT NO.:	25	28
REASON:	Subject was dropped prior to oxycodone dosing due to an adverse event.	Subject was dropped prior to oxycodone dosing due to an adverse event.
PERIOD:	2	2
REPLACEMENT:	N	N

Adverse Events:

Fourteen subjects experienced a total of thirty-five (35) adverse events during this study. All medical events were moderate. The adverse events were judged as 5 probably drug-related, 14 possibly drug-related, 2 unlikely drug-related, and 14 unrelated to drug-treatment (page 1890-1891, volume B3.7).

DURING STUDY ASSAY VALIDATION FOR NON-FASTING STUDY*
(Not to be released Under FOI)

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	[]
Inter Day Precision (%CV)		
Inter Day Accuracy (% of change)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

*The information on pages 1997-1998, volume B3.7.

Pharmacokinetic:

The plasma concentrations and pharmacokinetic parameters of oxycodone under non-fasting conditions were analyzed using SAS-GLM procedure for analysis of variance.

PK Results:

Mean Plasma Concentrations: Table 5, Figure 2

Pharmacokinetic Parameters: Tables 6 and 7

Geometric T/R Ratios (n=23):
 AUC0-t 0.97
 AUC0-inf 0.97
 Cmax 0.89

Comments:

- There were no measurable drug concentrations at 0 hr. There was no observation of first measurable drug concentration as Cmax.
- The T/R geometric mean ratios for AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25.
- The reviewer recalculated pharmacokinetic parameters. The reported values are in agreement with those obtained by the reviewer.
- The firm reported that 90% confidence intervals for log transformed AUC0-t, AUC0-inf, and Cmax are within acceptable limits of 80-125%, but they are not currently required by DBE for non-fasting BE studies.
- Subject #15, vomited approximately 1.33 hr after dosing (reference treatment, period 1). Subject #21, vomited approximately 10 hrs after dosing (reference treatment, period 1), and 10.5 hrs after dosing (test treatment, period 2). According to the CDER Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" (10/2000), subjects #15, and 21, should be deleted from the statistical analysis. However, if subjects #15, and 21 are included in the statistical analysis, the outcome decision on the application will remain the same (see Table #8).

Conclusion: The post-prandial bioequivalence study is acceptable.

Formulation (Not to be released under FOI)

- Formulation information is provided in Table 10.
- All inactive ingredients in the formulation were present at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

Dissolution (Not to be released under FOI)

- The dissolution information is provided in Tables #10-14, below.
- The firm proposes dissolution testing in 900 mL of Simulated Intestinal Fluid without enzyme using USP 24 apparatus I (basket) at 100 rpm. The test product should meet the following tentative specifications:

Time	Mean (% of claim)
1 hour	_____
4 hours	_____
8 hours	NLT _____

- For the sake of consistency, the Division of Bioequivalence proposes the following method (The innovator method):

Media: Simulated gastric fluid without enzyme
Volume: 900 mL
Apparatus: USP Apparatus 1 (Basket) at 100 rpm

Based on the firm's submitted dissolution data (Table #10), the DBE proposes the following specifications.

1 hour	_____
4 hours	_____
12 hours	NLT _____

- The dissolution testing is acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

RECOMMENDATIONS:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Teva Pharmaceuticals USA, on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg (lot #1313-157), comparing it to Purdue Pharma's OxyContin® Extended Release Tablet, 80 mg (lot #7J3N1), have been found acceptable by the Division of Bioequivalence. These studies demonstrate that the test product, Teva's Oxycodone Hydrochloride Extended Release Tablet, 80 mg, are bioequivalent to the reference product, Pharma's OxyContin® Extended Release Tablet, 80 mg, under fasting and non-fasting conditions.
2. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Teva Pharmaceuticals USA, on its Oxycodone Hydrochloride Extended Release Tablet, 160 mg (lot #1404-003), comparing it to Purdue Pharma's OxyContin® Extended Release Tablet, 160 mg (lot #9V51), have been found acceptable by the Division of Bioequivalence. These studies demonstrate that the test product, Teva's Oxycodone Hydrochloride Extended Release Tablet, 160 mg, are bioequivalent to the reference product, Pharma's OxyContin® Extended Release Tablet, 160 mg, under fasting and non-fasting conditions.
3. The dissolution testing conducted by the firm on its Oxycodone Hydrochloride Extended Release Tablet, 80 mg (lot #1313-157) and 160 mg (lot #1404-003), is acceptable.
4. 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 simulated gastric fluid without enzyme at 37°C using USP Apparatus 1 (basket) at 100 rpm. The test product should meet the following tentative specifications:

1 hour _____
4 hours _____
12 hours NLT _____

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

Acting RD INITIALLED MGOKHALE *mamali Gokhale* Date *3/7/02*
FT INITIALLED MGOKHALE

Concur: *Dale P. Conner*
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: *3/7/2002*

Table #1
Mean Plasma Concentrations (ng/mL)
of Oxycodone Under Fasting Conditions (n=27)

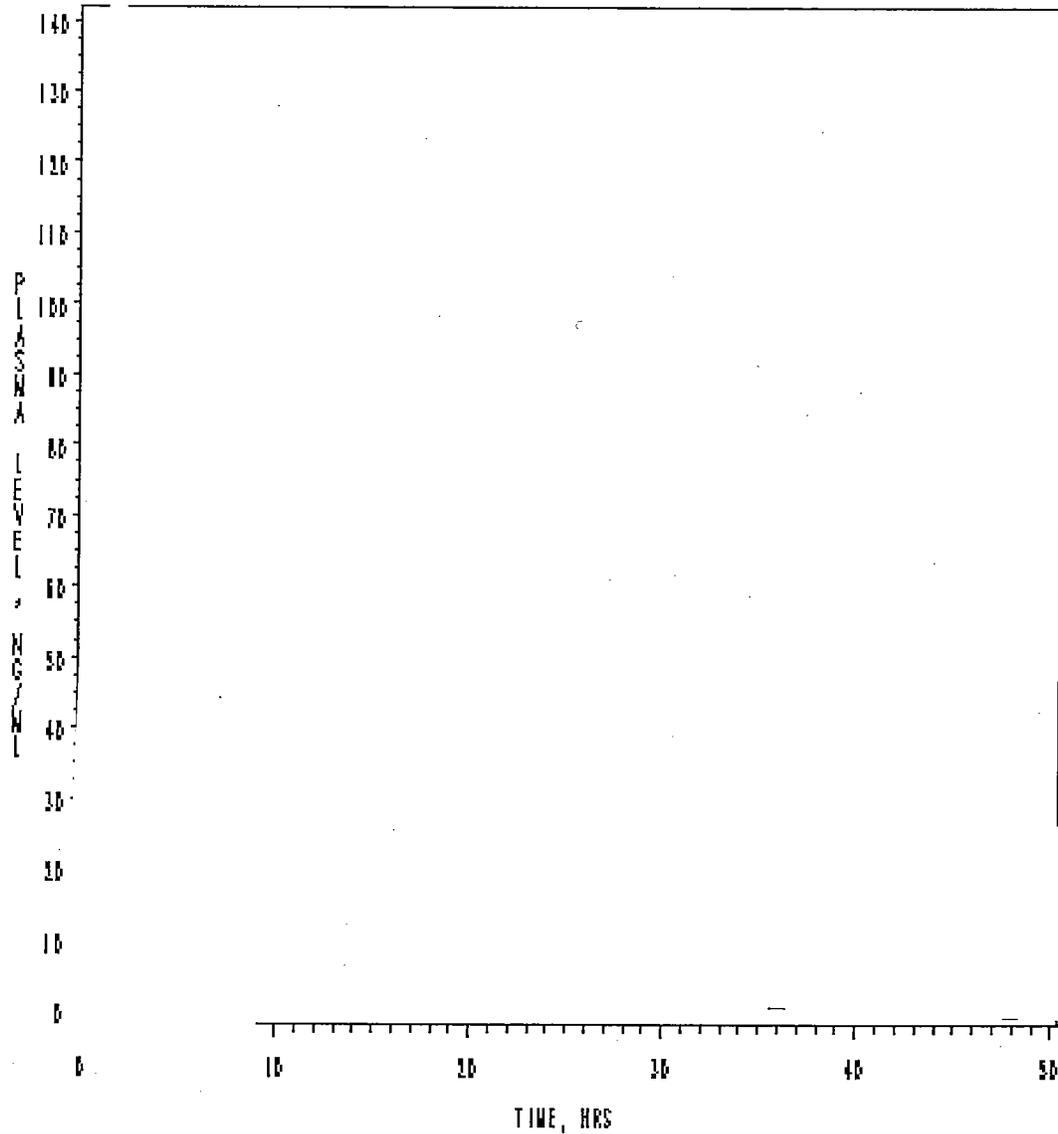
	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	19.56	11.51	32.29	21.42	0.61
1	57.56	17.61	91.42	28.37	0.63
2	95.15	21.71	128.34	28.25	0.74
3	108.40	25.76	130.22	29.63	0.83
4	118.81	26.34	129.25	30.17	0.92
5	126.49	28.55	125.61	30.51	1.01
6	120.45	30.54	114.49	27.88	1.05
7	107.55	21.82	104.87	25.95	1.03
8	100.12	31.36	99.78	24.21	1.00
10	80.37	22.82	82.82	25.03	0.97
12	65.66	21.29	63.17	21.96	1.04
16	40.53	16.72	37.77	17.18	1.07
24	13.64	7.97	10.48	6.23	1.30
36	2.35	2.11	1.74	1.48	1.35
48	0.56	0.65	0.40	0.43	1.38

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R
 UNITS: PLASMA LEVEL=NG/ML, TIME=HRS

**APPEARS THIS WAY
 ON ORIGINAL**

FIG P-1. PLASMA OXYCODONE LEVELS

OXYCODONE HCL ER TABLETS, 160 MG, ANGA #71-160
UNDER FASTING CONDITIONS
DOSE=1 X 160 MG



T&T ***1 8881

1=TEST (TEVA) 2=REF (PURDUE-PHARMA LP)

Table #2
Summary of Pharmacokinetics Parameters (Oxycodone)
Under Fasting Conditions* (n=27)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1653.87	476.61	1693.58	477.04	0.98
AUCT	1647.55	473.14	1676.15	470.82	0.98
C _{MAX}	129.96	28.20	137.54	28.79	0.94
KE	0.14	0.03	0.16	0.03	0.92
THALF	5.00	0.90	4.64	1.00	1.08
T _{MAX}	4.97	0.98	3.27	1.11	1.52

UNITS: AUC=NG HR/ML, C_{MAX}=NG/ML, T_{MAX}=HR, T/2=HR

*The values represent the arithmetic means.

Table #3
LSMeans and 90% Confidence Intervals
(Oxycodone, Under Fasting Conditions) (n=27)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1586.17	1617.39	0.98	93.43	102.95
LAUCT	1580.54	1613.80	0.98	93.56	102.52
LC _{MAX}	127.23	134.71	0.94	89.87	99.27

LSM1=LS mean test LSM2=LS mean reference

Low CI 12=Lower C.I. for T/R

UPP CI 12=Upper C.I. for T/R

UNIT: AUC=NG HR/ML

C_{MAX}=NG/ML

* The statistical analysis excluded subject #28 (vomited)

Table #4
LSMeans and 90% Confidence Intervals*
(Oxycodone, Under Fasting Conditions) (n=28)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1567.44	1619.70	0.97	91.83	101.99
LAUCT	1561.97	1616.17	0.97	91.99	101.54
LC _{MAX}	126.52	135.32	0.93	88.86	98.37

LSM1=LS mean test LSM2=LS mean reference

Low CI 12=Lower C.I. for T/R

UPP CI 12=Upper C.I. for T/R

UNIT: AUC=NG HR/ML

C_{MAX}=NG/ML

* The statistical analysis included subject #28 (vomited)

Table #5
Mean Plasma Concentrations (ng/mL)
of Oxycodone Under Non-Fasting Conditions (n=23)

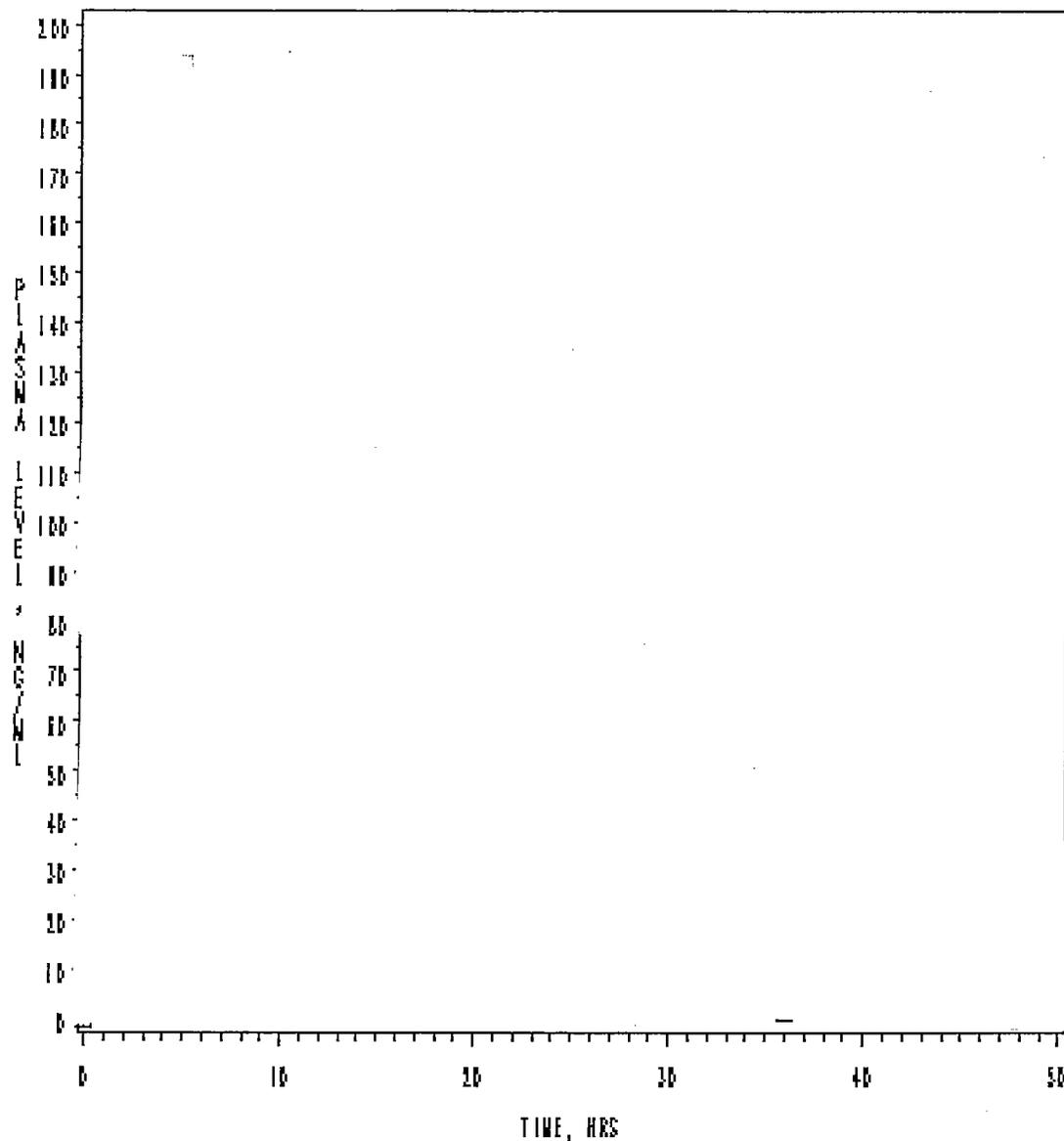
	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	4.17	4.38	10.29	13.15	0.41
1	24.97	17.86	47.33	37.16	0.53
2	110.47	49.12	135.38	54.99	0.82
3	154.33	60.65	181.13	57.97	0.85
4	160.01	53.86	189.90	51.83	0.84
5	171.91	70.21	192.61	52.83	0.89
6	161.30	49.14	169.17	48.35	0.95
7	141.43	45.54	144.97	51.83	0.98
8	126.86	38.82	131.75	52.95	0.96
10	97.73	33.96	89.53	35.60	1.09
12	69.71	31.14	62.80	28.85	1.11
16	35.72	18.65	32.01	17.48	1.12
24	9.92	6.32	8.52	5.73	1.16
36	1.47	1.35	1.30	1.39	1.14
48	0.26	0.36	0.24	0.42	1.12

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R
 UNITS: PLASMA LEVEL=NG/ML, TIME=HRS

**APPEARS THIS WAY
ON ORIGINAL**

FIG P-2 . PLASMA OXYCODONE LEVELS

OXYCODONE HCL ER TABLETS, 160 MG, ANDA #71-113
UNDER NON-FASTING CONDITIONS
DOSE=1 X 160 MG



TRT **** | □□□ 1

1=TEST(TEVA) 2=REF(PURDUE-PHARMA LP)

Table #6
Summary of Pharmacokinetics Parameters (Oxycodone)
Under Non-Fasting Conditions* (n=23)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1856.96	670.85	1915.11	658.61	0.97
AUCT	1853.61	669.19	1910.83	656.80	0.97
C _{MAX}	187.74	58.93	207.67	51.66	0.90
KE	0.16	0.02	0.17	0.03	0.99
THALF	4.31	0.64	4.30	0.73	1.00
T _{MAX}	4.74	0.96	4.26	0.96	1.11

UNITS: AUC=NG HR/ML, C_{MAX}=NG/ML, T_{MAX}=HR, T/2=HR

*The values represent the arithmetic means.

Table #7
LSMeans Ratios and 90% Confidence Intervals*
(Oxycodone, Under Non-Fasting Conditions) (n=23)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1756.45	1808.64	0.97	93.20	101.19
LAUCT	1753.34	1804.50	0.97	93.28	101.22
LC _{MAX}	179.32	201.28	0.89	83.68	94.86

LSM1=LS mean test LSM2=LS mean reference

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML

RLSM12=LS mean test/LS mean reference

*The statistical analysis excluded subject #15, and 21 (vomited).

Table #8
LSMeans Ratios and 90% Confidence Intervals*
(Oxycodone) (n=25)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	1757.10	1690.36	1.04	92.24	117.15
LAUCT	1753.99	1686.37	1.04	92.28	117.23
LC _{MAX}	177.44	201.92	0.88	82.80	93.26

LSM1=LS mean test LSM2=LS mean reference

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML

RLSM12=LS mean test/LS mean reference

* The statistical analysis included subject #15, and 21 (vomited).

Redacted _____

*10/17
Amulatus*

Page(s) of trade

secret and /or

confidential

commercial

information

Dissolution Methods / Results

(information on pages 116-133, volume B3.2)

Table #10

Dissolution Method: USP

Dissolution Medium: **Simulated gastric fluid without enzymes**

Volume: 900 mL

Dissolution Apparatus: 1 (basket)

		Test		REFERENCE		
		Lot No.: 1404-003		Lot No.: 9V51		
		Strength: 160 mg tab		Strength: 160 mg tab		
		No. of Units: 12		No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
30	16.89	[]	4.08	34.44	[]	1.17
60	26.55		4.24	48.17		1.06
120	42.13		3.57	64.91		0.85
240	65.48		1.9	84.46		0.93
480	91.13		0.73	103.51		0.73
720	99.45		0.83	107.14		0.82

Table#11

Dissolution Method: USP

Dissolution Medium: **Simulated intestinal fluid without enzymes**

Volume: 900 mL

Dissolution Apparatus: I (Basket)

		Test		REFERENCE		
		Lot No.: 1404-003		Lot No.: 9V51		
		Strength: 160 mg tab		Strength: 160 mg tab		
		No. of Units: 12		No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
30	18.68	[]	4.33	33.9	[]	1.78
60	28.35		3.58	46.5		1.44
120	43.38		3.22	61.68		1.23
240	64.61		1.33	79.42		1.08
480	88.26		0.83	97.23		0.93
720	97.22		0.8	103.77		0.74

Table#12						
Dissolution Method: USP						
Dissolution Medium: Phosphate buffer pH 3.0						
Volume: 900 mL						
Dissolution Apparatus: I (Basket)						
	Test Lot No.: 1404-003 Strength: 160 mg tab No. of Units: 12			REFERENCE Lot No.: 9V51 Strength: 160 mg tab No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
30	18.42	[]	4.92	36.25	[]	1.39
60	28.58		4.27	50.43		0.93
120	44.49		3.52	67.22		0.85
240	67.6		1.54	86.33		0.9
480	91.41		0.85	104.22		0.7
720	98.82		1.24	108.54		0.66

Table#13						
Dissolution Method: USP						
Dissolution Medium: Acetate buffer pH 5.0						
Volume: 900 mL						
Dissolution Apparatus: I (Basket)						
	Test Lot No.: 1404-003 Strength: 160 mg tab No. of Units: 12			REFERENCE Lot No.: 9V51 Strength: 160 mg tab No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
30	17.66	[]	5.67	35.18	[]	1.03
60	27.62		4.99	48.9		0.59
120	42.9		4.19	65.12		0.73
240	64.57		2.38	83.58		0.66
480	87.89		1.4	101.34		0.68
720	96.97		1.33	106.73		0.86

APPEARS THIS WAY
ON ORIGINAL

Table#14						
Dissolution Method: USP						
Dissolution Medium: Water						
Volume: 900 mL						
Dissolution Apparatus: I (Basket)						
	Test Lot No.: 1404-003 Strength: 160 mg tab No. of Units: 12			REFERENCE Lot No.: 9V51 Strength: 160 mg tab No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
30	18.46	[]	6.59	33.55	[]	1.24
60	27.48		9.38	46.41		0.74
120	42.63		7.36	61.89		0.71
240	64.27		5.03	79.08		0.74
480	84.48		4.85	94.68		0.77
720	89.15		4.68	97.9		0.83

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-168 APPLICANT: TEVA Pharmaceuticals USA

DRUG PRODUCT: Oxycodone HCl Extended Release Tablet, 80 mg, 160 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs: The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme at 37°C using USP Apparatus 1 (basket) at 100 rpm. The test product should meet the following tentative specifications:

1 hour	_____
4 hours	_____
12 hours	NLT _____

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,



for

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

CC: ANDA #76-168
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Bio team Leader

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Endorsements: (Final with Dates)
HFD-658/ Z. Wahba *ZW 3/7/02*
HFD-658/ M. Gokhale *MSK 3/7/02*
HFD-650/ D. Conner *for Rev 3/7/2002*

BIOEQUIVALENCY - Acceptable submission date: May 08, 2001

- | | |
|---------------------------------------------------------|---------------------------------|
| 1. Study Amendment, 01/11/02 | Strength: 80 mg
Outcome: AC |
| 2. Fasting Study (STF), 07/25/01
Clinical Sit: _____ | Strength: 160 mg
Outcome: AC |
| 3. Food Study (STP), 07/25/01
Clinical Sit: _____ | Strength: 160 mg
Outcome: AC |

Outcome Decisions: AC – Acceptable

**APPEARS THIS WAY
ON ORIGINAL**

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-168 SPONSOR : Teva Pharmaceuticals
DRUG AND DOSAGE FORM: Oxycodone Extended-Release Tablets
STRENGTH(S): 80 mg, 160 mg
TYPES OF STUDIES: Single-dose fasting and postprandial studies.
CLINICAL STUDY SITE: _____
ANALYTICAL SITE: _____
STUDY SUMMARY: Acceptable fasting and postprandial studies (for the 80 mg and 160 mg strengths)

DISSOLUTION: The dissolution data for the 80 mg and 160 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: <u>No</u>	Inspection status:	Inspection results:
First Generic <u>No</u> New facility <u>No</u> For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Zakaria Z. Wahba BRANCH: III

INITIAL: ZZW DATE: 3/7/02

TEAM LEADER: Mamata Gokhale, Ph.D BRANCH: III

INITIAL: MSK DATE: 3/7/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DP DATE: 11/4/02

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

**ADMINISTRATIVE
DOCUMENT(S)**

Telecon Record

Date: 9/10/01
ANDA: 76-168
Firm: TEVA Pharmaceuticals USA
Drug: Oxycodone Hydrochloride Tablets, 160 mg
FDA Participants: Paras Patel
Industry Participants: Philip Erickson
Phone: 215-591-3000

Agenda:

1. Paras requested the following information:

- The firm has to submit a citizen's petition to determine if Oxycontin® Tablets 160 mg by Purdue Pharma has been withdrawn for reasons of safety and/or efficacy.

The electronic Orange Book and current available cumulative supplement has not yet entered Purdue Pharma's Oxycontin® Tablets 160 mg in the discontinued section.

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

ANDA #: 76-168
DATE: June 19, 2001
TIME: 9:30 am
DRUG: Oxycodone HCl ER Tablets
FIRM: Mr. Philip Erickson for TEVA Pharmaceuticals USA
FDA PARTICIPANTS: Emily Thomas
PHONE NUMBER: 215-591-3141
TOPIC: Data needed

I asked Philip to provide a clarification on three items for this application. The patent certification needs to be revised to remove 4 of the 6 patents addressed, there are only 2 patents covering the 80 mg product. Also on the FDA Form 3455 there was no box checked off as to their financial certification, so I'm not sure if it is needed at all, according to FDA Form 3454 I don't believe there were any arrangements made. Lastly, the COA and information needed for inactive ingredient colliodal silicon dioxide is missing. Philip agreed to look into these items and amend or clarify the information for me. He will fax in the information needed with 10 business days and follow with a hard copy.

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-168

CORRESPONDENCE



Corporate Headquarters:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.

Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

May 8, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

505(L)(2)(A) OK
05-JUL-2001
[Handwritten signatures]

Bioequivalence Electronic Document



ORIGINAL ABBREVIATED NEW DRUG APPLICATION
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 23 volumes; 11 for the archival copy and 12 for the review copy. Two separately bound copies of the finished product analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg manufactured by TEVA Pharmaceuticals USA to the reference listed drug, OxyContin® (oxycodone controlled-release tablets), 80 mg under both fasting and post-prandial conditions.

An Entry and Validation Application format Bioequivalence ESD for the above referenced original new drug application will be provided under separate cover in the near future.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jb
Enclosures

76-168



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

PE

Phone: (215) 591 3000
FAX: (215) 591 8600

June 1, 2001

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**BIOEQUIVALENCE ELECTRONIC
SUBMISSION DOCUMENT**

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
BIOEQUIVALENCE ELECTRONIC SUBMISSION DOCUMENT

Dear Mr. Buehler:

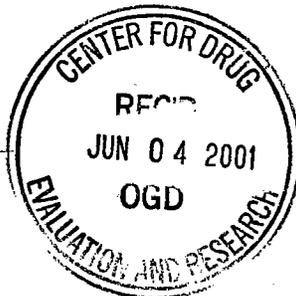
Reference is made to our original abbreviated new drug application dated May 8, 2001 for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg.

We submit herewith a Bioequivalence Electronic Submission Document (Entry and Validation Application) for the above referenced original abbreviated new drug application. TEVA Pharmaceuticals USA hereby declares that the data contained in the electronic submission is identical to that included in the paper submission. Any differences have been noted in the accompanying companion document.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson
PE/jb
Enclosures





Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NEW CORRESP
NC

July 3, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

Handwritten signature: Emily Thomas
10/11/01
7/9/01

ANDA #76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
NEW CORRESPONDENCE

Dear Mr. Buehler:

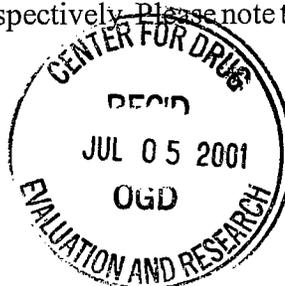
We submit herewith a new correspondence to the above-referenced pending ANDA in response to a June 19, 2001 telephone request made by Emily Thomas of your office to Philip Erickson, Director of Regulatory Affairs, TEVA USA. Ms. Thomas phoned regarding several items needed for completion of the review for acceptance of our filing dated May 8, 2001. The items are addressed below in the order in which they were presented in the aforementioned conversation.

1. Ms. Thomas commented that a raw material procedure manual and Certificate of



purposes.

2. Form 3455: Disclosure: Financial Interests and Arrangements of Clinical Investigators was inadvertently provided. As requested, copies of the "Statement of Financial Interests" are included in **Attachment 1** for _____ Principal Investigator of _____ The enclosed forms are intended to replace pages 135 and 137 respectively. Please note that their pagination matches that of the original submission.



3. In deference to your request for a revised Patent Certification, we wish to merely provide clarification. Our Patent Certification was originally presented based on the assumption that U.S. Patent 4,861,598, U.S. Patent 4,970,075, U.S. Patent 5,266,331 and U.S. Patent 5,549,912 were submitted for listing in the Orange Book for this Reference Listed Drug (RLD), but for some reason were not listed. Should it be determined that the aforementioned patents are not applicable to the involved RLD, we commit to revise our certification as necessary. To further support the above assumption is the fact that currently distributed innovator labeling for the RLD lists each of these patents.

If there are any further questions, please do not hesitate to contact me at (215)591-3141 or via facsimile at (215)591-8812.

Sincerely,



PE/jb

Enclosures

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-168

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
|||||

JUL -5 2001

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.

Reference is made to the telephone conversation dated June 19, 2001 and your correspondence dated July 3, 2001.

NAME OF DRUG: Oxycodone Hydrochloride Extended-release Tablets,
80 mg

DATE OF APPLICATION: May 8, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 8, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

- 1) Each owner of the patent or the representative designated by the owner to receive the notice.
- 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
- 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter

immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

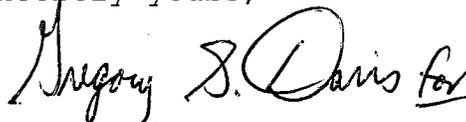
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Jeon Min
Project Manager
(301) 827-5849

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

July 25, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalence Electronic Submission Document

ORIG AMENDMENT

N/A C

505616211 OK
26-SEP-2001
Jeffrey S. Davis
- firm has submitted a CP asking the Agency to relist the 160mg strength.

ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
UNSOLICITED AMENDMENT - ADDITION OF 160 mg STRENGTH

Dear Mr. Buehler:

We submit herewith an amendment to our above-referenced pending abbreviated new drug application for the addition of the 160 mg strength of the drug product OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS to this file. Please note that this submission is presented in the basic format of an ANDA for ease of your review.

In support of this amendment, we have provided Chemistry, Manufacturing, and Controls (CMC) documentation relevant to the 160 mg strength and updated CMC documentation applicable to the 80 mg tablets.

Two separately bound copies of the finished product analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 160 mg manufactured by TEVA Pharmaceuticals USA to the reference listed drug, OxyContin® (oxycodone controlled-release tablets), 160 mg under both fasting and post-prandial conditions.

An Entry and Validation Application format Bioequivalence ESD for the above referenced original new drug application will be provided under separate cover in the near future.



ANDA # 76-168

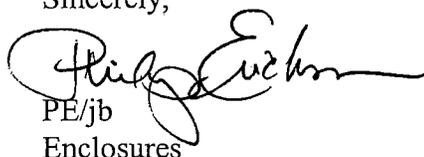
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

UNSOLICITED AMENDMENT-ADDITION OF .160 mg STRENGTH

PAGE 2 of 2

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,


PE/jb
Enclosures

APPEARS THIS WAY
ON ORIGINAL



Corporate Headquarters:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3000
 FAX: (215) 591 8600

August 3, 2001

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP

NC

ANDA # 76-168
 OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
 RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) and 21 CFR 314.95

Dear Mr. Buehler:

TEVA Pharmaceuticals USA provided a Notice of Certification of Non-Infringement of U.S. Patent Nos. 4,861,598, 4,970,075, 5,266,331, 5,549,912, 5,508,042 and 5,656,295 to the holder of NDA 20-553 for OxyContin®, Purdue Pharma L.P., in accord with 214.95(b). In addition, a courtesy copy was provided to the patent assignee, Euro-Celtique, S.A., Luxembourg.

The purpose of this communication is to request clearance to provide Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by Euro-Celtique, S.A., Luxembourg, in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e).

Your review of this request is appreciated. Response to this request may be made to my attention or by telephone at (215) 591-3141 or via facsimile at (215)591-8812.

Sincerely,

Philip Erickson

PE/jb
 Enclosure



8/16/01
 - As per conversation with Peter Rickman, I contacted firm and stated that agency will accept Federal Express Documentation - Also stated in future agency excepts prior request to use Federal Express of Patent Notification.
Paras Patel
8/16/01

Please file in latest
open archival volume

76-168



FACSIMILE

TEVA PHARMACEUTICALS USA

FAX: (215) 591-8812

1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454

Phone: (215) 591-3000

TO: Lt. Greg Davis	DATE: August 23, 2001
COMPANY: FDA	
FAX NUMBER: 301-594-1174	FROM: Philip Erickson, R.Ph.
NO. OF PAGES: 1	DIRECT LINE: 215-591-3141

4-1
Patel

ANDA # 76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) and 21 CFR 314.95

Dear Lt. Davis:

TEVA Pharmaceuticals USA is providing a Notice of Certification of Non-Infringement of U.S. Patent Nos. 4,861,598, 4,970,075, 5,266,331, 5,549,912, 5,508,042 and 5,656,295 to the holder of NDA 20-553 for OxyContin[®], Purdue Pharma L.P., in accord with 214.95(b) with regard to the 160 mg strength. In addition, a copy is being provided to the patent assignee, Euro-Celtique, S.A., Luxembourg.

The purpose of this communication is to inform you of our intent to utilize Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by Euro-Celtique, S.A., Luxembourg, in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e). We refer you to your previous approval of this request as made for the 80 mg strength on 7/19/01. Conditions of this arrangement have not changed, nor have the parties involved, only the strength of product.

Response to this correspondence may be made to my attention or by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson, R.Ph.

Director, Regulatory Affairs, Solid Oral Dosage Forms

OK to use Fed Ex.

02-NOV-2001

PROMPT DELIVERY IS APPRECIATED

NOTICE: The documents accompanying this telecopy transmission from TEVA Pharmaceuticals USA contains information belonging to the sender. The information is intended only for the use of the individual or entity named above. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify the sender by telephone to arrange for the return of the original document.

Redacted 2

*dated
9/10/01
ldr*

Page(s) of trade

secret and /or

confidential

commercial

information

LAW OFFICES

KLEINFELD, KAPLAN AND BECKER

1140 NINETEENTH STREET, N.W.

WASHINGTON, D. C. 20036-6606

TELEPHONE (202) 223-5120

FACSIMILE (202) 223-5619

E-MAIL: kkb@kkblaw.com

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KINSEY S. REAGAN
PETER R. MATHERS
BONNIE A. BEAVERS
DANIEL R. DWYER
GLENN E. DAVIS
PRESCOTT M. LASSMAN
STACY L. EHRlich
JENNIFER A. DAVIDSON
STACEY L. VALERIO
ROBERT O. WINTERS

WEST COAST OFFICE:
ONE MARKET STREET
STEUART TOWER, SUITE 1450
SAN FRANCISCO, CA 94105-1313
TELEPHONE (415) 538-0014
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD
1907-1993

ALAN H. KAPLAN
1930-2001

OF COUNSEL:
HARVEY A. SUSSMAN

November 5, 2001

**NOTIFICATION OF FILING OF ACTION
FOR PATENT INFRINGEMENT**

NC
WAZ
P. P. P. 11/9/01
NEW OFFICE

Office of Generic Drugs (HFD-600)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773



RE: ANDA No. 76-168
Oxycodone Hydrochloride
Extended-Release Tablets, 80 mg

Dear Sir or Madam:

Pursuant to Section 314.107(f)(2) of the regulations, this is to notify you that an action for patent infringement relevant to the above referenced ANDA No. 76-168 was filed by the patent owners on September 14, 2001.

On or about August 6, 2001, the owners of patents 4,861,598 ('598 patent), 4,970,075 ('075 patent), 5,266,331 ('331 patent), 5,549,912 ('912 patent), 5,656,295 ('295 patent), and 5,508,042 ('042 patent) listed in the Orange Book for OxyContin® (Oxycodone Hydrochloride Extended-Release Tablets) received notice pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act ("the Act") dated August 3, 2001 from Teva Pharmaceuticals USA, Inc., applicant for the above referenced ANDA.

Based on the submission of the above referenced ANDA, Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc. and The Purdue Pharma Company (the patent owners of the '912 patent, the '042 patent and the '295 patent) on September 14, 2001, filed a complaint against Teva Pharmaceuticals USA, Inc. for infringement of these patents in the United States District Court for the Southern District of New York, Case Number 01-CIV-8507.

KLEINFELD, KAPLAN AND BECKER

Office of Generic Drugs (HFD-600)

November 5, 2001

Page 2

Under Section 505(j)(5)(B)(iii) of the Act and Section 314.107(b)(3) of the regulations, based on the filing of this action, the above referenced application may not be made effective until February 6, 2004 (i.e., 30 months from August 6, 2001), unless the court extends or reduces this period.

Yours very truly,



Richard S. Morey
Peter R. Mathers

Counsel for Purdue Pharma L.P.,
The Purdue Frederick Company,
The P.F. Laboratories, Inc. and
The Purdue Pharma Company





Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NAT *P.M.P.*
12/11/01

November 15, 2001

NEW CORRESP
NC

PATENT INFORMATION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY
CLOCK/LEGAL STATUS-US PATENT Nos. 4,861,598; 4,970,075; 5,266,331; 5,549,912;
5,508,042; and 5,656,295

Dear Mr. Buehler:

Teva Pharmaceuticals USA (Teva) hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent Nos. 4,861,598; 4,970,075; 5,266,331; 5,549,912; 5,508,042; and 5,656,295 was provided to Purdue Pharma L.P., as the holder of NDA 20-553 for OxyContin® 80 mg Tablets, and Euro-Celtique, S.A., as the owner of the patents, in accord with 314.95(c).

Please note that an August 3, 2001 request to provide Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by Euro-Celtique, S.A., Luxembourg, in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e), was approved by Peter Rickman of the Agency on August 16, 2001.

In accord with 21 CFR 314.95(e), Teva is hereby providing documentation of the receipt of the above-referenced August 3, 2001 Notice of Certification for U.S. Patent Nos. 4,861,598; 4,970,075; 5,266,331; 5,549,912; 5,508,042; and 5,656,295 (**Attachment 1**). In accord with 314.95(f), the first day of the 45-day period provide for in section 505(j)(4)(B)(iii) of the Act is August 7, 2001, the first day after the receipt of Notice. Therefore, the 45-day period ended on September 20, 2001.



ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg

RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY CLOCK/LEGAL STATUS-US PATENT Nos. 4,861,598; 4,970,075; 5,266,331; 5,549,912; 5,508,042; and 5,656,295

Page 2 of 2

We hereby inform the Agency of a suit filed by Purdue Pharma L.P. against Teva concerning U.S. Patent Nos. 5,549,912; 5,508,042; and 5,656,295. The suit, Civil Action No. E014, was filed on September 14, 2001 in the Southern District Court of New York. The aforementioned suit was filed within the 45-day period. Teva hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 2**.

If there are any questions regarding the information presented herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb

Enclosures



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

September 21, 2001

NC
NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CORRESPONDENCE TO A PENDING APPLICATION

ANDA # 76-168
OXYCODONE HYDROCHLORIDE EXTENDED RELEASE TABLETS, 80mg
CORRESPONDENCE TO A PENDING APPLICATION

Dear Mr. Buehler:

In accord with a telephone conversation with Paras Patel this morning we are providing a copy of the Citizen Petition from _____ dated September 18, 2001 requesting determination of withdrawal of the RLD 160 mg product. Hard copy will follow via Federal Express. _____ has also been requested to forward original hard copy.

Should you have any questions or comments, please do not hesitate to contact me by phone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/m
Enclosure



MODE = MEMORY TRANSMISSION

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END=JUN-07 10:22

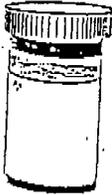
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-FDA CDER OGD LPS -

***** - *****

Fax Cover Sheet



Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Generic Drugs
 Rockville, Maryland

Date: June 7, 02
 To: Phillip Erickson
 Phone: 215-591-3141 Fax: 215-591-8818

From: Chan Park
 Phone: (301) 827-5846 Fax: (301) 443-3847

Number of Pages: 8
 (including Cover Sheet)

Comments: ANDA 76-168
Labeling Comments. Thanks,
Chan

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.



NAI
gr 1/12/02

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

January 8, 2002

NEW CORRESP

NC

NAI
MMS
1-10-02

PATENT INFORMATION

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

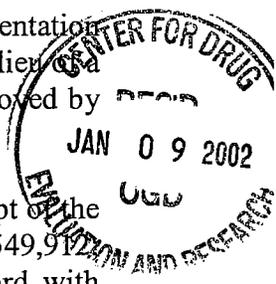
ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY
CLOCK/LEGAL STATUS-US PATENT Nos. 5,549,912; 5,508,042; 5,656,295; 4,861,598;
4,970,075 and 5,266,331

Dear Mr. Buehler:

TEVA Pharmaceuticals USA (TEVA) hereby certifies that a Notice of Certification of Non-Infringement for U.S. Patent Nos. 5,549,912; 5,508,042; 5,656,295; 4,861,598; 4,970,075 and 5,266,331 was provided to Purdue Pharma L.P., as the holder of NDA 20-553 for OxyContin® 160 mg Tablets, and Euro-Celtique, S.A., as the owner of the patents, in accord with 314.95(c).

Please note that an August 23, 2001 request to provide Federal Express Tracking Documentation as evidence of receipt of Notice of Certification by Euro-Celtique, S.A., Luxembourg, in lieu of a United States Postal Service return receipt, in accord with 21 CFR 314.95(e), was approved by Lt. Greg Davis of the Agency on November 2, 2001.



In accord with 21 CFR 314.95(e), TEVA is hereby providing documentation of the receipt of the above-referenced November 8, 2001 Notice of Certification for U.S. Patent Nos. 5,549,912; 5,508,042; 5,656,295; 4,861,598; 4,970,075 and 5,266,331 (**Attachment 1**). In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is November 14, 2001, the first day after the receipt of Notice. Therefore, the 45-day period ended on December 28, 2001.

We hereby inform the Agency of a suit filed by Purdue Pharma L.P. against TEVA concerning U.S. Patent Nos. 5,549,912; 5,508,042 and 5,656,295. The suit, Civil Action No. CV 11212, was filed on December 6, 2001 in the Southern District Court of New York. The aforementioned suit was filed within the 45-day period. TEVA hereby commits to provide notification of the

gr
1/15/02

ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg

RECEIPT OF NOTICE OF CERTIFICATION OF NON-INFRINGEMENT/END OF 45-DAY CLOCK/LEGAL

STATUS-US PATENT Nos. 5,549,912; 5,508,042; 5,656,295; 4,861,598; 4,970,075 and 5,266,331

Page 2 of 2

outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 2**.

No action for infringement of U.S. Patent Nos. 4,861,598; 4,970,075 and 5,266,331 within the meaning of section 505(j)(5)(B)(iii) of the Act was brought against TEVA within the required 45-day period. Resultant from Purdue Pharma L.P. failing to undertake legal action within the 45-day period, they have waived their right to pursue future legal endeavors under the scope of the Waxman-Hatch Act regarding these patents.

If there are any questions regarding the information presented herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb

Enclosures



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

January 11, 2002

ORIG AMENDMENT

N/A C

MAJOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
MAJOR AMENDMENT-RESPONSE TO OCTOBER 24 and NOVEMBER 2, 2001 REVIEW
LETTERS

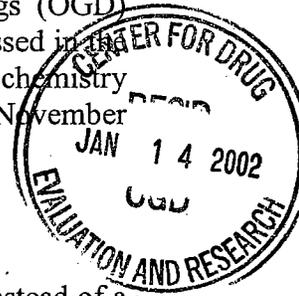
Dear Mr. Buehler:

We submit herewith a major amendment to the above-referenced pending ANDA. The subject of this amendment is our response to comments from the Office of Generic Drugs (OGD) pertaining to this application. The bioequivalency response to your comment is addressed in the order in which it was presented in your review letter dated October 24, 2001 and the chemistry comments and updated labeling are provided in response to your review letter dated November 2, 2001. Copies of these two letters are enclosed in **Attachment 1**.

Bioequivalency Deficiency

A two-way crossover design study was done for the fasting bioequivalence study instead of a replicate design, which deviated from the October 2000 *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations*. Discussions were held with the Contract Research Organization (CRO) and the Investigational Review Board (IRB) associated with the fasting study regarding the risk to human volunteers enrolled as subjects.

A common hazard with many opioid analgesics is respiratory depression. To try to avoid this hazard, each study volunteer was administered 50 mg of Naltrexone, 15 hours prior to dosing, followed by another 50 mg, 3 hours prior to dosing. Typically, patients not currently taking opioids are started with doses of 10 mg every 12 hours. The volunteers of this study received 80 mg at each dosing period and to minimize the risk for the



volunteers, a two way crossover design was employed. As such, each volunteer received two 80 mg doses instead of the four doses required by a replicate design study.

Additionally, the two-way crossover study design was compared to a replicate study design. Since the statistical endpoint was to be achieved through average bioequivalence calculations for both types of studies, the two-way crossover study would be expected to yield comparable results to the replicate design.

Chemistry & Labeling:

A. Deficiencies

1. As requested, the ~~specification~~ specification has been revised from ~~testing~~ testing to ~~as the mean value for all samples tested, with an RSD of NMT~~ as the mean value for all samples tested, with an RSD of NMT
2. In response to your request that we implement a control test to ensure that the tablet



below.

Tablets	Loss On Drying (average of 2 tests)
_____	_____
_____	_____

* Testing was performed 7 months after ~~_____~~ process

Although the ~~_____~~ LOD result was generated 7 months after the ~~_____~~ process, it is a worst case scenario in that the tablets were stored in the warehouse exposed to desiccants. The tablets stored in these bottles would not be expected to lose any additional moisture. Additionally, the product's acceptable stability results further demonstrate that the differences in LOD are insignificant. Please note that the parameters for the coating process will be validated to further ensure that the tablets will be subjected to comparable moisture as that experienced by the pivotal batch.

3. The stability limit for total impurities has been reduced from NMT ~~_____~~ to NMT ~~_____~~, to be consistent with the data obtained. The updated stability limit may be found in the Finished Product Stability Protocol provided in **Attachment 2**. An updated Finished Product Procedures Manual also containing the revised specification is provided in **Attachment 3**.

4. Updated stability data for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg is provided in **Attachment 2**.

B. Acknowledgments

1. We acknowledge that results of the establishment evaluation request and review of the in-vivo bioequivalence studies are pending.
2. Samples will be available upon request for methods validation, which will be conducted by the appropriate FDA Regional Laboratory.
3. The title of the analytical testing procedure has been revised. A copy of the Oxycodone Hydrochloride Extended-Release Tablets, 80 mg and 160 mg Finished Product Procedures Manual (Version 3.0) is provided in **Attachment 3**. Please note that all references to strengths other than the 80 mg and 160 mg have been removed.
4. We acknowledge that our July 25, 2001 amendment for the addition of 160 mg strength has changed the status of our application to a MAJOR amendment and that the amendment will be reviewed when we respond to the above deficiencies.

C. Labeling Deficiencies

Four copies of draft insert labeling and four copies of draft product container (100s) labeling, which incorporates the revisions recommended from the Labeling Branch's November 2, 2001 review letter, are enclosed in **Attachment 4**. To facilitate review of this submission and in accord with 21 CFR 314.94(a)(8)(iv), we have provided a comparison document of our proposed labeling with that of our last submission in **Attachment 5**. This comparison annotates both minor format changes and the revisions recommended in your deficiency comments.

We acknowledge that further changes in our labels and/or labeling based upon changes in the approved labeling of listed drug may be made upon further review of the application prior to approval. We also acknowledge that final printed labeling will not be requested until the Agency responds to the Citizen Petition regarding Oxycontin[®] (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg.

The information provided herein represents, in our opinion, a complete response to your letters of October 24 and November 2, 2001 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb

Enclosures



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

May 7, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NW/gm
ORIG AMENDMENT
MINOR AMENDMENT

ANDA # 76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
MINOR AMENDMENT – RESPONSE TO APRIL 5, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA. The subject of this amendment is our response to comments from the Office of Generic Drugs (OGD) pertaining to this application. Our response to the chemistry comments presented in your review letter dated April 5, 2002 are presented first followed by the response to the labeling comments. A copy of this letter is enclosed in **Attachment 1**.

Chemistry Deficiencies:

We acknowledge that the Division of Chemistry has no further questions at this time and that our Bioequivalence Amendment dated January 11, 2002 is still under review by the Division of Bioequivalence. We note that any changes made to the chemistry, manufacturing and controls section of our application as a result of outstanding bioequivalency deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

We also note that no final action regarding our application will be taken until a final decision has been reached regarding our Citizen's Petition dated September 18, 2001.

Labeling Deficiencies:

1. We acknowledge that labeling comments specifically associated with our proposed 160 mg tablets will be deferred until the Agency responds to the Citizen Petition regarding Oxycontin® (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg.

RECEIVED
MAY 08 2002
OGD / ODER

NW
5/14/02

2. CONTAINER - 100s

- a. In conformance with 21 CFR 1302.06, we assure that our container systems include a tamper-evident seal. The seal used is _____, manufactured by _____ ✓
- b. Please note that we are still seeking approval of the 160 mg tablets and we refer you to the draft container labels for the 160 mg strength in our amendment for the addition of the 160 mg strength submitted on July 25, 2001. Four copies of 160 mg strength draft container (100s) labeling, which incorporates the revisions recommended from the Labeling Branch's November 2, 2001 review letter, are provided in **Attachment 2**. ✓

3. PATIENT INFORMATION LEAFLET

- a. Four copies of the proposed draft patient information leaflet in accordance with the patient information leaflet approved on January 15, 2002 for the reference listed drug are provided in **Attachment 3**. Two patient information leaflets will be supplied for the 100s container size. The leaflets will be provided by attaching them to the package insert. *perfection* ✓
- b. The full text of the patient information leaflet is reprinted at the end of the insert labeling and referred to in the PRECAUTIONS, Information for Patients subsection. ✓

4. INSERT

- a. Please note that all of the inactive ingredients in our formulation are listed in our insert. _____ corresponds to the listing for _____ . The four digit number refers to the percentage content of the _____ groups, calculated on a _____ . The substitution type (_____) does not alter the inactive ingredient itself, and therefore is not specified on our package insert. _____ is the preferred name for Triacetin by the European Pharmacopoeia. This name is not listed on our package insert, as the USP preferred name is Triacetin.
- b. The Head Injury subsection was added immediately after the "Respiratory depression" subsection of DRUG ABUSE AND ADDICTION. All labeling comments are addressed in the four copies of the proposed draft insert labeling provided in **Attachment 4**.

In accordance with 21 CFR 314.94 (a) (8) (iv), a side-by-side comparison of our proposed labeling with our last submission (or with the reference listed drug as applicable) with all differences annotated and explained is provided in **Attachment 5**.

This information is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb
Enclosures



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

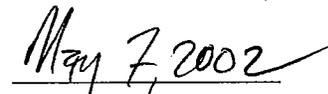
Phone: (215) 591 3000
FAX: (215) 591 8600

**OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS,
80 mg and 160 mg**

MINOR AMENDMENT – RESPONSE TO APRIL 5, 2002 REVIEW LETTER

In accord with the 21 CFR 314.94(d)(5), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.


Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms


Date



Administrative Offices
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591-3141
Fax: (215) 591-8812

June 25, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

~~ORIG AMENDMENT~~
N/A

LABELING AMENDMENT

ANDA #76-168

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
LABELING AMENDMENT – RESPONSE TO JUNE 7, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated June 7, 2002 from the Labeling Review Branch. For ease of review, a copy of the review letter is included in **Attachment 1**.

Labeling Deficiencies:

1. Container – 100s
 - a. We have increased the prominence of the statement, “for use in opioid tolerant patients” as requested.
 - b. It is TEVA Pharmaceuticals USA’s practice to differentiate our drug products of different strengths by using contrasting colors.

Please find four copies of draft container labels and a comparison to our previous revision in **Attachment 2**.

2. The insert has been revised as requested. Four copies of draft package insert labeling and a comparison to our previous revision is provided in **Attachment 3**.

RECEIVED

JUN 26 2002

OGD / CDER

3. We have removed the comment referring to the “ ” from the patient information leaflet as it does not apply to our drug product, as requested. Please find four copies of draft patient information leaflet as well as a comparison to our previous revision in **Attachment 4**.

We acknowledge that final printed insert labeling will not be requested until an adequate response is provided to our Citizen Petition regarding Oxycontin[®] (Oxycodone Hydrochloride) Extended-Release Tablets, 160 mg.

This information is submitted for your continued review of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb

Enclosures



Administrative Offices:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

December 4, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

NC

BIOAVAILABILITY

ANDA #76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 12, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a review letter dated November 12, 2002 from the Division of Bioequivalence and a telephone conversation on November 25, 2002 with Steven Mazzella of the Division of Bioequivalence. The referenced review letter is provided in **Attachment 1** for ease of review.

Per your request, a Finished Product Procedures Manual and Stability Protocol are provided in **Attachment 2** which contain updated Drug Release specifications.

We note that the bioequivalency comments provided in the communication are preliminary and subject to revision after review of the entire application.

The information herein represents, in our opinion, a complete response to the November 12, 2002 review letter and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

RECEIVED

DEC 06 2002

OGD / CDER



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

**OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS,
80 mg and 160 mg**

**TELEPHONE AMENDMENT – RESPONSE TO NOVEMBER 12, 2002 REVIEW
LETTER**

In accord with the 21 CFR 314.94(d)(5), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Dec 4, 2002
Date



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

July 2, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT

NIAF

ANDA #76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
LABELING AMENDMENT – RESPONSE TO MAY 30, 2003 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated May 30, 2003 from the Labeling Review Branch. For ease of review, a copy of the review letter is included in **Attachment 1**.

Labeling Deficiencies:

1. General Comment

- a. The storage temperature statement has been revised to read “Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP)” as per TEVA format.
- b. The container label has been revised as requested. Twelve copies of final printed labels and a comparison to our previous revision are provided in **Attachment 2**.

2. Insert

- a. In accord with 21 CFR 201.57 (f)(2), the full text of the patient information leaflet is reprinted at the end of our package insert. Therefore, the name and address of our business along with the revision date is included at the end of the package insert.

The insert has been revised as requested. Twelve copies of final printed package insert, labeling and a comparison to our previous revision are provided in **Attachment 3**.

RECEIVED

JUL 03 2003

OGD/CDER

3. Patient Information Leaflet

- a. Each container of 100 tablets will have one patient information leaflet glued to the bottle along with the package insert.

The patient information leaflet has been updated as requested. Please find twelve copies of the final printed patient information leaflet as well as a comparison to our previous revision in **Attachment 4**.

This information is submitted for your continued review of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Ericsson, M.D.

PE/jb

Enclosures



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3141
 FAX: (215) 591 8812

December 19, 2003

ORIG AMENDMENT
N/AM

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

**MINOR AMENDMENT -
 FINAL APPROVAL REQUESTED**

ANDA 76-168
 OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
 MINOR AMENDMENT – FINAL APPROVAL REQUESTED

RECEIVED

DEC 22 2003

OGD / CDER

Dear Mr. Buehler:

We submit herewith a Minor Amendment - Final Approval Requested to the above-referenced ANDA in accord with a letter from the Office of Generic Drugs dated September 29, 2003 which granted tentative approval of this file. Updated information related to chemistry, manufacturing and controls data is provided as follows:

The ~~_____~~ has changed their name from ~~_____~~
 Please find a cover letter stating this name change in **Attachment 1**. An updated letter of authorization for DMF No. ~~_____~~ is also provided in **Attachment 1** reflecting this name change.

The raw material chromatographic purity method and specifications have been updated to accommodate the use of the raw material manufacturer's specifications for known and unknown impurities. The following table summarizes the old specifications vs. the new specifications:

Old	New
Individual Impurities NMT	Individual Unknown Impurity NMT
Total Impurities NMT	NMT
	Total Impurities NMT

Please see **Attachment 2** for the updated Raw Material Procedures Manual (Version 2.0) and **Attachment 3** for the accompanying cross validation report titled "Oxycodone Hydrochloride, USP Assay and Chromatographic Purity Cross Validation Protocol".

The Finished Product Laboratory Procedures Manual was updated to remove the 160 mg strength for clarity purposes (**Attachment 4**).

The Finished Product Stability Protocol provided in **Attachment 5** was updated to remove reference to the 160 mg strength product. An updated 24 month Stability Summary Report for the 80 mg strength is provided in **Attachment 6**.

Please note that final printed labeling (container labels, package insert and patient information leaflet) was provided in our July 2, 2003 Labeling Amendment.

The information provided herein is submitted towards the continued review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jb

APPEARS THIS WAY
ON ORIGINAL



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

**OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS,
80 mg**

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

In accord with the 21 CFR 314.96 (b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.



Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

December 19, 2003
Date



MAI
2/24/04
ML

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

February 18, 2004

ORIG AMENDMENT

ML/AM

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
AMENDMENT -RISK MANAGEMENT PROGRAM COMMITMENT/REQUEST FOR
FINAL APPROVAL

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced tentatively approved ANDA in accord with the recommendations received from the agency during a teleconference on February 12, 2004. Specifically, we wish to convey our agreement to provide the agency with a comprehensive Risk Management Program proposal, that reflects refinements to that which we had previously submitted, for your consideration. This proposal will be submitted within one month after receipt of final approval of our ANDA. Additionally, we agree to provide a finalized Risk Management Program (RMP) within two months of receipt of final approval. Our RMP will address the four key elements presented by the agency as they pertain to our intended market audience and will incorporate appropriate changes based on any comments received by Teva after review of our proposal. Having provided these commitments in accord with your recent request, we respectfully request final approval of ANDA 76-168 without further delay. Should you have additional questions or comments please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,


PE

RECEIVED
FEB 19 2004
OGD/CDER

FILE IN ANDA 76-168



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3142
FAX: (215) 591 8812

March 5, 2004

NEW CORRESP
MC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 76-168 OXYCODONE EXTENDED RELEASE TABLETS, 80 mg
PROPOSED RISK MANAGEMENT PROGRAM

Dear Mr. Buehler:

Enclosed is Teva's proposed Risk Management Program (RMP) prepared in accord with comments provided to us during the February 12, 2004 teleconference. Teva has made every effort to incorporate Dr. Rappaport's recommendations and we believe that the proposed RMP will prove to be an effective safeguard in the market place and add to Purdue's program in an effort to prevent abuse, misuse, addiction, overdose and diversion of oxycodone ER tablets. Seven copies are provided in order to accommodate a multi-office review (five under separate cover mailed directly to Ted Palat.)

We look forward to action on this proposal within the one month timeframe committed to in the February 12 call. Teva stands ready to address any comments or questions.

Sincerely,

DAJ
Enclosure

RECEIVED
MAR 08 2004
UGD/CDER



OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

APPLICANT: TEVA Pharmaceuticals

TEL:

ATTN: Philip Erickson

FAX: 215-591-8812

FROM: Ted Palat

PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 8, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride Extended-release Tablets, 80 mg.

We are pleased to inform you that this application is **TENTATIVELY APPROVED!**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

 8/29/03



Administrative Offices:
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

May 5, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

ORIG AMENDMENT

N/A

ANDA # 76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg and 160 mg
NEW CORRESPONDENCE – REQUEST FOR WITHDRAWAL OF 160 mg STRENGTH

Dear Mr. Buehler:

We hereby submit a new correspondence to the above-referenced abbreviated new drug application to respectfully request the withdrawal of Oxycodone Hydrochloride ER Tablets 160 mg from this application.

Additionally, please find enclosed newly created draft insert labeling that is specific to only the 80 mg extended release strength.

This information is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/cj
Enclosures

RECEIVED
MAY 6 - 2003
OGD / CDER

Handwritten initials and date: 5/9/03



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

ANDA # 76-168

**OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS,
80 mg and 160 mg**

NEW CORRESPONDENCE – REQUEST FOR WITHDRAWAL OF 160 mg STRENGTH

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

5/5/03
Date

MODE = MEMORY TRANSMISSION

START=MAY-30 13:09

END=MAY-30 13:11

FILE NO.=001

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Fax Cover Sheet

Department of Health and Human Services
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Generic Drugs
 Rockville, Maryland



Date: May 30, 03
 To: Philip Erickson
 Phone: 215-591-3141 Fax: 215-591-8810
 From: Chan Park

Phone: 301-827-5846 Fax: 301-443-3847

Re: ANDA 76-168

Number of Pages: _____
 (Including Cover Sheet)

Comments:

*Labeling deficiencies per the phone call.
 Thanks,
 Chan*

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NAI
2/10/04
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Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3142
FAX: (215) 591 8812

January 29, 2004

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AM

ANDA #76-168
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg
TELEPHONE AMENDMENT – RESPONSE TO JANUARY 23, 2004 REQUEST

Dear Mr. Buehler:

We submit this telephone amendment to the above-referenced tentatively approved ANDA for the purpose of providing Teva's plan for a Risk Management Program (RMP) for Oxycodone HCl Extended-Release Tablets. The program was designed to incorporate the elements that you communicated in a teleconference call with Philip Erickson on January 23, 2004. A description of Teva's RMP is herewith enclosed.

It is Teva's understanding from documents published from the DEA, the GAO and the FDA that RMPs are optional but strongly encouraged for the marketing of opioid products. Based on this, Teva is working diligently to implement our program. Also, based on the optional nature of RMPs, Teva fully anticipates receiving final approval of ANDA 76-168 on February 6, 2004, which is the end of the 30-month stay period.

We therefore submit our planned program for your review with our commitment to implement the program promptly pending any comments you may have on the content.

Lastly, Teva is concurrently submitting comments to the Petition for Stay of Approval filed by Purdue Pharma. These comments include further rationale for Teva's position with regard to our eligibility for approval on February 6, 2004 as well as justification for our position that the petition lacks merit and should be denied.

Please review our RMP plan and provide any comments that you may have. Independent of this review, we expect final approval of this application on February 6, 2004.

RECEIVED

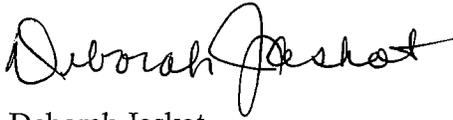
JAN 30 2004

OGD/CDER

ANDA #76-168
Oxycodone HCl ER Tablets, 80 mg
Telephone Amendment

Should you have any questions regarding the information contained herein, please contact me directly at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,



Deborah Jaskot
Executive Director, Regulatory Affairs

Enclosures

cc: Daniel Troy