CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-264

Name: Naltrexone HCl Tablets USP, 25 mg, 50 mg and 100 mg

Sponsor: Mallinckrodt, Inc.

Approval Date: March 22, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

APPROVAL LETTER

ANDA 76-264

MAR 22 2002

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd
P.O. Box 5840
St. Louis, MO 63134

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Naltrexone Hydrochloride Tablets USP, 25 mg, 50 mg, and 100 mg.

Reference is also made to your amendments dated February 11, and February 18, 2002.

We note that the 25 mg and 100 mg strengths of this drug product were included in the application through the ANDA Suitability Petition process. A Suitability Petition for these strengths was submitted under Section 505(j)(2)(C) of the Act, and approved on April 13, 2000.

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 Naltrexone Hydrochloride Tablets, USP 50 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Revia® Tablets, 50 mg of Bristol Myers Squibb Pharmaceutical Company). In addition, your Naltrexone Hydrochloride Tablets USP, 25 mg and 100 mg, can be expected to have the same therapeutic effect as that of equivalent doses of Revia Tablets. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

Sincerely yours,

Robert Lee Test /for 3/22/2002

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

cc: ANDA 76-264
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-640/D.Roselle/ D Roselle 3/6/02
HFD-647/G.Smith/ 3/6/02
HFD-617/J.Min/ 3/15/02
HFD-613/C.Park/ C Park 3/18/02
HFD-613/C.Hoppes/3/4/02 3/18/02

V:\FIRMSAM\MALLINCKRODT\LTRS&REV\76264.APD.doc

F/T by rad3/5/02

APPROVAL

conc satisfactory.
Howard Sapuen
3/19/02

Robert W West
3/19/2002
pending EES for
Mallinckrodt facility.
(Fume acceptable 3/20/02)
RW
3/22/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

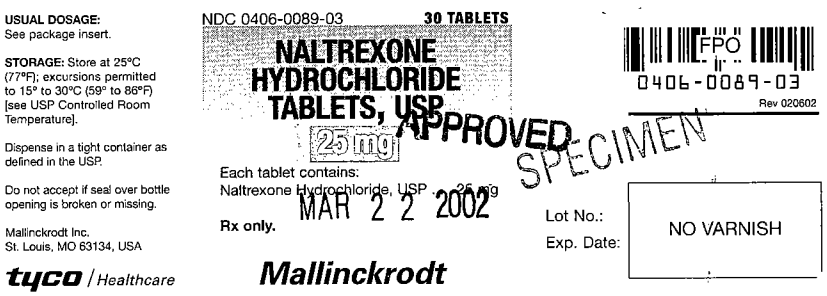
APPROVED LABELING

Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

25 mg, 30-count Bottle

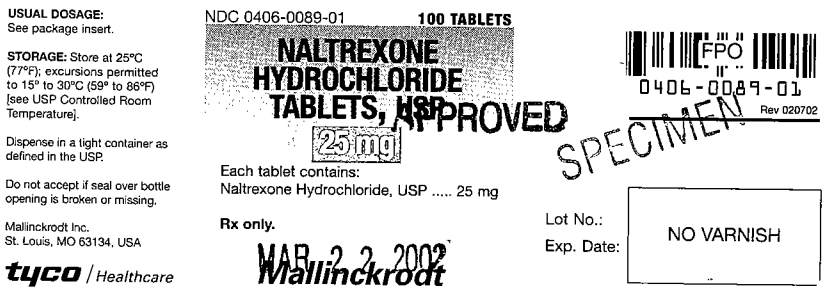


Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

25 mg, 100-count Bottle



Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

25 mg, 1000-count Bottle

USUAL DOSAGE:
See package insert.

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

Dispense in a tight container as defined in the USP.

Do not accept if seal over bottle opening is broken or missing.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

tyco / Healthcare

NDC 0406-0089-10 **1000 TABLETS**

NALTREXONE HYDROCHLORIDE TABLETS, USP

APPROVED

25 mg

Each tablet contains:
Naltrexone Hydrochloride, USP ..... 25 mg

Rx only. MAR 2 2 2002

Mallinckrodt

FPO
0406-0089-10
Rev 020802

SPECIMEN

Lot No.:
Exp. Date:

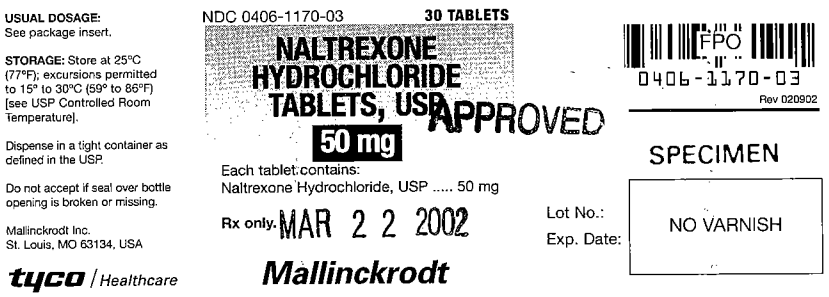
NO VARNISH

Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

50 mg, 30-count Bottle

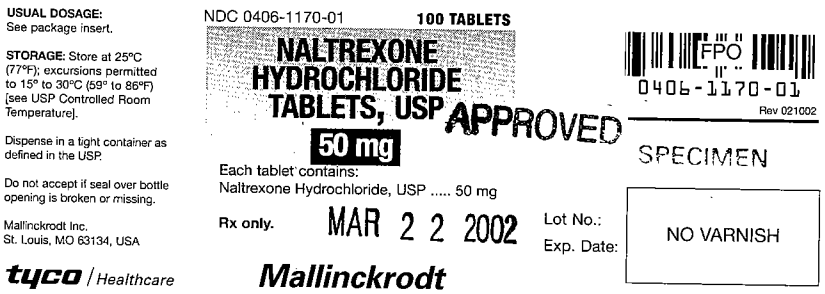


Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

50 mg, 100-count Bottle



Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

50 mg, 1000-count Bottle

USUAL DOSAGE:
See package insert.

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

Dispense in a tight container as defined in the USP.

Do not accept if seal over bottle opening is broken or missing.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

tyco / Healthcare

NDC 0406-1170-10 **1000 TABLETS**

NALTREXONE HYDROCHLORIDE TABLETS, USP

50 mg

APPROVED

Lot No.:
Exp. Date:

Each tablet contains:
Naltrexone Hydrochloride, USP ... 50 mg

Rx only.

MAR 2 2 2002

SPECIMEN

Mallinckrodt

FPO
0406-1170-10
Rev 021102

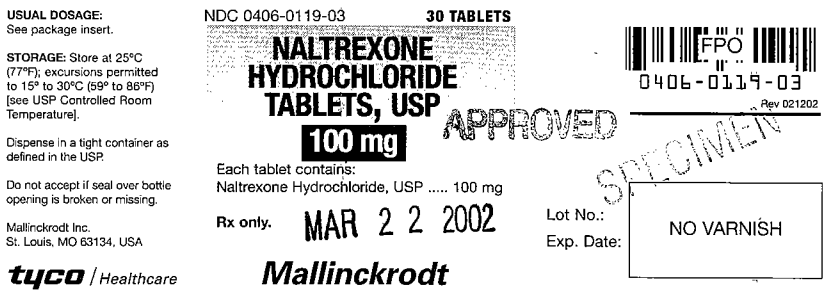
NO VARNISH

Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

100 mg, 30-count Bottle



Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

100 mg, 100-count Bottle

USUAL DOSAGE:
See package insert.

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

Dispense in a tight container as defined in the USP.

Do not accept if seal over bottle opening is broken or missing.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

tyco / Healthcare

NDC 0406-0119-01 **100 TABLETS**

NALTREXONE HYDROCHLORIDE TABLETS, USP

100 mg

APPROVED SPECIMEN

Each tablet contains:
Naltrexone Hydrochloride, USP ... 100 mg

Rx only MAR 2 2 2002

Mallinckrodt

FPO
0406-0119-01
Rev 021302

Lot No.:
Exp. Date:

NO VARNISH

Original

Final Printed Labeling

Naltrexone Hydrochloride Tablets, USP

100 mg, 1000-count Bottle

USUAL DOSAGE:
See package insert.

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

Dispense in a tight container as defined in the USP.

Do not accept if seal over bottle opening is broken or missing.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

tyco / Healthcare

NDC 0406-0119-10 **1000 TABLETS**

NALTREXONE HYDROCHLORIDE TABLETS, USP

100 mg APPROVED

Each tablet contains:
Naltrexone Hydrochloride, USP ... 100 mg

Rx only.

MAR 2 2 2002

Mallinckrodt

FPO
0406-0119-10
Rev 021402

SPECIMEN

Lot No.:
Exp. Date:

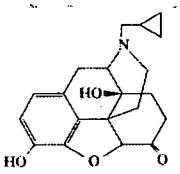
NO VARNISH

Naltrexone Hydrochloride Tablets, USP
(25 mg, 50 mg and 100 mg)
Rx only

DESCRIPTION

Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone hydrochloride is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone. Naltrexone hydrochloride has the chemical name of 17-(cyclopropylmethyl)-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride.

It has the following structural formula:



NALTREXONE $C_{20}H_{23}NO_4 \cdot HCl$ MW=377.86

Naltrexone hydrochloride is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. Naltrexone Hydrochloride Tablets, USP for oral administration are available as film coated tablets, containing 25 mg, 50 mg, or 100 mg of naltrexone hydrochloride.

In addition, each tablet contains the following inactive ingredients: crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, silicon dioxide, titanium dioxide, yellow iron oxide and red iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamic Actions: Naltrexone is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids.

When co-administered with morphine, on a chronic basis, naltrexone blocks the physical dependence to morphine, heroin and other opioids.

Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of naltrexone is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, naltrexone will precipitate withdrawal symptomatology.

Clinical studies indicate that 50 mg of naltrexone hydrochloride will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of naltrexone hydrochloride provides blockade for 48 hours, and tripling the dose of naltrexone hydrochloride provides blockade for about 72 hours.

Naltrexone blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of naltrexone in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone has been shown to reduce alcohol consumption in clinical studies.

Naltrexone is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics: Naltrexone is a pure opioid receptor antagonist. Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5% to 40%. The activity of naltrexone is believed to be due to both parent and the 6-β-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (T-1/2) values for naltrexone and 6-β-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-β-naltrexol are dose proportional in terms of AUC and C_{max} over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

Absorption: Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-β-naltrexol occur within one hour of dosing.

Distribution: The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. *In vitro* tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Metabolism: The systemic clearance (after intravenous administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extra-hepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-β-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

Elimination: The renal clearance for naltrexone ranges from 30 to 127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6-β-naltrexol ranges from 230 to 369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impairment: Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion (see **Metabolism** above). Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted (see **PRECAUTIONS: Special Risk Patients**).

Clinical Trials:

Alcoholism: The efficacy of naltrexone as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double blind trials. These studies used a dose of naltrexone hydrochloride 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, dementia, and secondary psychiatric diagnoses were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either naltrexone hydrochloride 50

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PANEL 1 OF 6

mg once daily or placebo. In this study, naltrexone proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of naltrexone as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of naltrexone appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with naltrexone supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies. Naltrexone was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

Treatment of Opioid Addiction:

Naltrexone has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrate an unequivocally beneficial effect of naltrexone on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioral contract, or other compliance-enhancing protocol. Naltrexone, unlike methadone or LAAM (levo-alpha-acetyl-methadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under external conditions that support continued use of the medication.

Individualization of Dosage:

DO NOT ATTEMPT TREATMENT WITH NALTREXONE UNLESS, IN THE MEDICAL JUDGEMENT OF THE PRESCRIBING PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7 to 10 DAYS. IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST.

Treatment of Alcoholism:

The placebo-controlled studies that demonstrated the efficacy of naltrexone as an adjunctive treatment of alcoholism used a dose regimen of naltrexone hydrochloride 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not studied in these trials.

Physicians are advised that 5% to 15% of patients taking naltrexone for alcoholism will complain of non-specific side effects, chiefly gastrointestinal upset. Prescribing physicians have tried using an initial 25 mg dose, splitting the daily dose, and adjusting the time of dosing with limited success. No dose or pattern of dosing has been shown to be more effective than any other in reducing these complaints for all patients.

Treatment of Opioid Dependence:

Once the patient has been started on naltrexone hydrochloride, 50 mg once a day will produce adequate clinical blockade of the actions of parenterally administered opioids. As with many non-agonist treatments for addiction, naltrexone is of proven value only when given as part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

A flexible approach to a dosing regimen may be employed to enhance compliance. Thus, patients may receive 50 mg of naltrexone hydrochloride every weekday with a 100 mg dose on Saturday or patients may receive 100 mg every other day, or 150 mg every third day. Several of the clinical studies reported in the literature have employed the following dosing regimen: 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday. This dosing schedule appeared to be acceptable to many naltrexone patients successfully maintaining their opioid-free state.

Experience with the supervised administration of a number of potentially hepatotoxic agents suggests that supervised administration and single doses of naltrexone hydrochloride higher than 50 mg may have an associated increased risk of hepatocellular injury, even though three-times a week dosing has been well tolerated in the addict population and in initial clinical trials in alcoholism. Clinics using this approach should balance the possible risks against the probable benefits and may wish to maintain a higher index of suspicion for drug-associated hepatitis and ensure patients are advised of the need to report non-specific abdominal complaints (see **PRECAUTIONS: Information for Patients**).

INDICATIONS AND USAGE

Naltrexone hydrochloride tablets are indicated:

In the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

Naltrexone hydrochloride tablets have not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.

CONTRAINDICATIONS

Naltrexone is contraindicated in:

1) Patients receiving opioid analgesics.
2) Patients currently dependent on opioids, including those currently maintained on opiate agonists [e.g., methadone or LAAM (levo-alpha-acetyl-methadol)].
3) Patients in acute opioid withdrawal (see **WARNINGS**).
4) Any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids.
5) Any individual with a history of sensitivity to naltrexone or any other components of this product. It is not known if there is any cross-sensitivity with naloxone or the phenanthrene containing opioids.
6) Any individual with acute hepatitis or liver failure.

WARNINGS

Hepatotoxicity:

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

Evidence of the hepatotoxic potential of naltrexone is derived primarily from a placebo controlled study in which naltrexone hydrochloride was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In that study, 5 of 26 naltrexone recipients developed elevations of serum transaminases (i.e., peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values)

after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone is a direct (i.e., not idiosyncratic) hepatotoxin.

This conclusion is also supported by evidence from other placebo controlled studies in which exposure to naltrexone hydrochloride at doses above the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than did placebo. Transaminase elevations in 3 of 9 patients with Alzheimer's Disease who received naltrexone hydrochloride (at doses up to 300 mg/day) for 5 to 8 weeks in an open clinical trial have been reported.

Although no cases of hepatic failure due to naltrexone administration have ever been reported, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing naltrexone as they would other drugs with the potential for causing hepatic injury.

Unintended Precipitation of Abstinence:

To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7 to 10 days before starting naltrexone. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of naltrexone. The naloxone challenge test is described in the DOSAGE AND ADMINISTRATION section.

Attempt to Overcome Blockade:

While naltrexone is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by naltrexone is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opiate blockade (**see PRECAUTIONS, Information for Patients**).

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.

Ultra Rapid Opioid Withdrawal:

Safe use of naltrexone in rapid opiate detoxification programs has not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General:

When Reversal of Naltrexone Blockade is Required: In an emergency situation in patients receiving fully blocking doses of naltrexone, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction) presumably due to histamine release.

Irrespective of the drug chosen to reverse naltrexone blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Accidentally Precipitated Withdrawal: Severe opioid withdrawal syndromes precipitated by the accidental ingestion of naltrexone have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of naltrexone and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required intravenous fluid administration. In all cases patients were closely monitored and therapy with non-opioid medications was tailored to meet individual requirements.

Use of naltrexone does not eliminate or diminish withdrawal symptoms. If naltrexone is initiated early in the abstinence process, it will not preclude the patient's experience of the full range of signs and symptoms that would be experienced if naltrexone had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients:

Renal Impairment: Naltrexone and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.

Hepatic Impairment: Caution should be exercised when naltrexone hydrochloride is administered to patients with liver disease. An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Suicide: The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with naltrexone (see **ADVERSE REACTIONS**).

Information for Patients: It is recommended that the prescribing physician relate the following information to patients being treated with naltrexone:

You have been prescribed naltrexone hydrochloride as part of the comprehensive treatment for your alcoholism or drug dependence. You should carry identification to alert medical personnel to the fact that you are taking naltrexone. A naltrexone medication card may be obtained from your physician and can be used for this purpose. Carrying the identification card should help to ensure that you can obtain adequate treatment in an emergency. If you require medical treatment, be sure to tell the treating physician that you are receiving naltrexone therapy.

You should take naltrexone as directed by your physician. If you attempt to self-administer heroin or any other opiate drug, in small doses while on naltrexone, you will not perceive any effect. Most important, however, if you attempt to self-administer large doses of heroin or any other opioid (including methadone or LAAM) while on naltrexone, you may die or sustain serious injury, including coma.

Naltrexone is well-tolerated in the recommended doses, but may cause liver injury when taken in excess or in people who develop liver disease from other causes. If you develop abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of your eyes, you should stop taking naltrexone immediately and see your doctor as soon as possible.

Laboratory Tests: A high index of suspicion for drug-related hepatic injury is critical if the occurrence of liver damage induced by naltrexone is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are recommended at a frequency appropriate to the clinical situation and the dose of naltrexone.

Naltrexone does not interfere with thin-layer, gas-liquid, and high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone or quinine in the urine. Naltrexone may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Please consult the test manufacturer for specific details.

Drug Interactions: Studies to evaluate possible interactions between naltrexone and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of naltrexone and other drugs is required.

The safety and efficacy of concomitant use of naltrexone and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethargy and somnolence have been reported following doses of naltrexone and thioridazine.

Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient receiving naltrexone, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged (see **PRECAUTIONS**).

Carcinogenesis, Mutagenesis and Impairment of Fertility: The following statements are based on the results of experiments in mice and rats. The potential carcinogenic, mutagenic and fertility effects of the metabolite 6-β-naltrexol are unknown.

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (600 mg/m^2/day; 16 times the recommended therapeutic dose, based on body surface area) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day (600 mg/m^2/day) was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay, and in non-specific DNA repair tests with *E. coli*. However, no evidence of genotoxic potential was observed in a range of other *in vitro* tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Naltrexone (100 mg/kg/day [600 mg/m^2/day] PO; 16 times the recommended therapeutic dose, based on body surface area) caused a significant increase in pseudopregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

Pregnancy: Category C. Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥ 30 mg/kg/day (180 mg/m^2/day; 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (720 mg/m^2/day; 18 times the recommended therapeutic dose, based on body surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (32 and 65 times the recommended therapeutic dose, respectively, based on body surface area).

Rats do not form appreciable quantities of the major human metabolite, 6-β-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

There are no adequate and well-controlled studies in pregnant women. Naltrexone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor And Delivery: Whether or not naltrexone affects the duration of labor and delivery is unknown.

Nursing Mothers: In animal studies, naltrexone and 6-β-naltrexol were excreted in the milk of lactating rats dosed orally with naltrexone. Whether or not naltrexone is excreted in human milk is unknown. Because many drugs are excreted in human milk, caution should be exercised when naltrexone is administered to a nursing woman.

Pediatric Use: The safe use of naltrexone in pediatric patients younger than 18 years old has not been established.

ADVERSE REACTIONS

During two randomized, double-blind placebo-controlled 12 week trials to evaluate the efficacy of naltrexone as an adjunctive treatment of alcohol dependence, most patients tolerated naltrexone well. In these studies, a total of 93 patients received naltrexone hydrochloride at a dose of 50 mg once daily. Five of these patients discontinued naltrexone because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of naltrexone in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of naltrexone use, placebo-controlled studies employing up to five-fold higher doses of naltrexone hydrochloride (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that naltrexone causes hepatocellular injury in a substantial proportion of patients exposed at higher doses (see **WARNINGS** and **PRECAUTIONS: Laboratory Tests**).

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate naltrexone, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid free." It is critical to recognize that naltrexone can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially opioid addiction, are at risk for multiple numerous adverse events and abnormal laboratory findings, including liver function abnormalities. Data from both controlled and observational studies suggest that these abnormalities, other than the dose-related hepatotoxicity described above, are not related to the use of naltrexone.

Among opioid free individuals, naltrexone administration at the recommended dose has not been associated with a predictable profile of serious adverse or untoward events. However, as mentioned above, among individuals using opioids, naltrexone may cause serious withdrawal reactions (see **CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION**).

Reported Adverse Events:

Naltrexone has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7 to 10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints (see **Individualization of Dosage**).

Alcoholism:

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

RATE RANGES OF NEW ONSET EVENTS

	Naltrexone	Placebo
Depression	0 to 15%	0 to 17%
Suicide Attempt/Ideation	0 to 1%	0 to 3%

Although no causal relationship with naltrexone is suspected, physicians should be aware that treatment with naltrexone does not reduce the risk of suicide in these patients (see **PRECAUTIONS**).

Opioid Addiction:

The following adverse reactions have been reported both at baseline and during the naltrexone clinical trials in opioid addiction at an incidence rate of more than 10%:

Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

The incidence was less than 10% for:

Loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

The following events occurred in less than 1% of subjects:

Respiratory: nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.

Cardiovascular: nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, tachycardia.

Gastrointestinal: excessive gas, hemorrhoids, diarrhea, ulcer.

Musculoskeletal: painful shoulders, legs or knees; tremors, twitching.

Genitourinary: increased frequency of, or discomfort during, urination; increased or decreased sexual interest.

Dermatologic: oily skin, pruritus, acne, athlete's foot, cold sores, alopecia.

Psychiatric: depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams.

Special senses: eyes-blurred, burning, light sensitive, swollen, aching, strained; ears-"clogged", aching, tinnitus.

General: increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding", inguinal pain, swollen glands, "side" pains, cold feet, "hot spells."

Post-marketing Experience: Data collected from post-marketing use of naltrexone show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a withdrawal syndrome. Events that have been reported include anorexia, asthenia, chest pain, fatigue, headache, hot flashes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnea, rash, increased sweating, and vision abnormalities.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, adrenal, or gonadal hormones. The clinical significance of such changes is not fully understood.

Adverse events, including withdrawal symptoms and death, have been reported with the use of naltrexone in ultra rapid opiate detoxification programs. The cause of death in these cases is not known (see **WARNINGS**).

Laboratory Tests: With the exception of liver test abnormalities (see **WARNINGS** and **PRECAUTIONS**), results of laboratory tests, like adverse reaction reports, have not shown consistent patterns of abnormalities that can be attributed to treatment with naltrexone.

Idiopathic thrombocytopenic purpura was reported in one patient who may have been sensitized to naltrexone in a previous course of treatment with naltrexone. The condition cleared without sequelae after discontinuation of naltrexone and corticosteroid treatment.

DRUG ABUSE AND DEPENDENCE

Naltrexone is a pure opioid antagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

OVERDOSAGE

There is limited clinical experience with naltrexone overdosage in humans. In one study, subjects who received 800 mg daily naltrexone hydrochloride for up to one week showed no evidence of toxicity.

In the mouse, rat and guinea pig, the oral LD_{50}s were 1,100 to 1,550 mg/kg; 1,450 mg/kg; and 1,490 mg/kg; respectively. High doses of naltrexone hydrochloride (generally ≥ 1,000 mg/kg) produced salivation, depression/reduced activity, tremors, and convulsions. Mortalities in animals due to high-dose naltrexone administration usually were due to clonic-tonic convulsions and/or respiratory failure.

Treatment Of Overdosage: In view of the lack of actual experience in the treatment of naltrexone hydrochloride overdose, patients should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date information.

DOSAGE AND ADMINISTRATION

IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST AND DO NOT INITIATE NALTREXONE THERAPY UNTIL THE NALOXONE CHALLENGE IS NEGATIVE.

Treatment of Alcoholism:

A dose of 50 mg once daily is recommended for most patients (see **Individualization of Dosage**). The placebo-controlled studies that demonstrated the efficacy of naltrexone hydrochloride as an adjunctive treatment of alcoholism used a dose regimen of naltrexone hydrochloride 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials.

A patient is a candidate for treatment with naltrexone if:

- the patient is willing to take a medicine to help with alcohol dependence
- the patient is opioid free for 7 to 10 days
- the patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal.)
- the patient is not allergic to naltrexone, and no other contraindications are present

Refer to **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** Sections for additional information.

Naltrexone should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with naltrexone were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

Treatment of Opioid Dependence:

Initiate treatment with naltrexone using the following guidelines:

1. Treatment should not be attempted unless the patient has remained opioid-free for at least 7 to 10 days. Self-reporting of abstinence from opioids in opioid addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.
2. If there is any question of occult opioid dependence, perform a naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with naltrexone should not be attempted. The naloxone challenge can be repeated in 24 hours.
3. Treatment should be initiated carefully, with an initial dose of 25 mg of naltrexone hydrochloride. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

Naloxone Challenge Test: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The naloxone challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous:
Inject 0.2 mg naloxone.
Observe for 30 seconds for signs or symptoms of withdrawal.
If no evidence of withdrawal, inject 0.6 mg of naloxone.
Observe for an additional 20 minutes.

Subcutaneous:
Administer 0.8 mg naloxone.
Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of naloxone. In some cases, 0.1 mg IV naloxone has produced a diagnostic response.

Interpretation of the Challenge: Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, backache, bone or joint pains, tremors, sensations of skin crawling, or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered.

Warning: If the test is positive, do NOT initiate naltrexone therapy. Repeat the challenge in 24 hours. If the test is negative, naltrexone therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold naltrexone and repeat the challenge in 24 hours.

Alternative Dosing Schedules:

Once the patient has been started on naltrexone hydrochloride, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (i.e., this dose will block the effects of a 25 mg intravenous heroin challenge). A flexible approach to a dosing regimen may need to be employed in cases of supervised administration. Thus, patients may receive 50 mg of naltrexone hydrochloride every weekday with a 100 mg dose on Saturday, 100 mg every other day, or 150 mg every third day. The degree of blockade produced by naltrexone may be reduced by these extended dosing intervals.

There may be a higher risk of hepatocellular injury with single doses above 50 mg, and use of higher doses and extended dosing intervals should balance the possible risks against the probable benefits (see **WARNINGS** and **Individualization of Dosage**).

Patient Compliance:

Naltrexone should be considered as only one of many factors determining the success of treatment. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, including medication compliance.

HOW SUPPLIED

Naltrexone Hydrochloride Tablets, USP 25 mg are available as a pink film coated capsule-shaped tablet with a convex surface, debossed with a number "25" on one side, and "DEPADE" on the other side.

Bottles of 30 .....NDC 0406-0089-03
Bottles of 100 .....NDC 0406-0089-01
Bottles of 1000 .....NDC 0406-0089-10

Naltrexone Hydrochloride Tablets, USP 50 mg are available as a yellow film coated capsule-shaped tablet with a convex surface, debossed with a number "50" and a full bisect in between the 5 and 0 on one side and "DEPADE" on the other side.

Bottles of 30 .....NDC 0406-1170-03
Bottles of 100 .....NDC 0406-1170-01
Bottles of 1000 .....NDC 0406-1170-10

Naltrexone Hydrochloride Tablets, USP 100 mg are available as a beige film coated capsule-shaped tablet with a convex surface, debossed with a number "100" and a partial score above and below the middle 0 on one side and a "DEPADE" with a partial score on the other side.

Bottles of 30 .....NDC 0406-0119-03
Bottles of 100 .....NDC 0406-0119-01
Bottles of 1000 .....NDC 0406-0119-10

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

tyco

Healthcare

Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.

Mallinckrodt

Printed in U.S.A.

Rev 032602

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

LABELING REVIEW(S)

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

ANDA Number: **76-264** Date of Submission: **October 31, 2001**

Applicant's Name: **Mallinckrodt, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets USP, 25 mg, 50 mg, & 100 mg**

Labeling Deficiencies:

1. CONTAINER - 30s, 100s, & 1000s

   a. Revise the storage temperature statement to read "Store at ———————

   b. Your proposed package size of 30s appears to be a unit-of -use packaging, which requires a child-resistant closure to comply with the Poison Prevention Packaging Act. Please assure that you employ a child-resistant closure for this package size and/or comment.

2. INSERT

   a. GENERAL

      It is preferable to use the term "to" rather than a hyphen to express a range of numerical numbers.

   b. DESCRIPTION

      i. First paragraph, last sentence

         ...4, 5α-epoxy-3, 14... [note "α"]

      ii. Add a bullet to the molecular formula to read "$C_{20}H_{23}NO_4$•HCL"

      iii. Revise the molecular weight to read "377.86" per USP 24.

      iv. Last paragraph - Revise to read:

         In addition, each tablet contains the following inactive ingredients: crospovidone...

   c. CLINICAL PHARMACOLOGY

      You may delete the term "hydrochloride" to read "naltrexone" throughout this section except where "naltrexone hydrochloride" is specifically associated with a dose of this product.

d. INDICATIONS AND USAGE

i. First paragraph:

Naltrexone hydrochloride tablets are...

ii. Naltrexone hydrochloride tablets have not...

e. CONTRAINDICATIONS - Item #2:

2) ...on opioids , including those currently maintained on opiate agonists [e.g., methadone or LAAM (levo-alpha-acetyl-methadol)].

f. WARNINGS

i. See comment under CLINICAL PHARMACOLOGY.

ii. Attempt to Overcome Blockade - First paragraph, last sentence:

...blockade (see **PRECAUTIONS, Information for Patients).**

g. PRECAUTIONS

i. See comment under CLINICAL PHARMACOLOGY.

ii. Information for Patients - Third paragraph, last sentence:

...other opioid (including methadone or LAAM) while on...

h. ADVERSE REACTIONS

See comment under CLINICAL PHARMACOLOGY.

i. DRUG ABUSE AND DEPENDENCE

Naltrexone is a pure...

j. HOW SUPPLIED

i. See comments under CONTAINER.

ii. Your description of 100 mg tablet is not consistent with the one found in your controls for Finished Dosage Form. Specifically, please clarify whether the side with "DEPADE" is partially scored or not

Please revise your container labels and insert labeling, as instructed above, and submit container labels and insert labeling in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
	Yes	No	N.A.
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage?		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review is based on the labeling for Revia® (DuPont, approved May 15, 2001). This is NDA 18-932/S-015.

2. This product is a subject of USP monograph.

3. The innovator has only 50 mg tablets approved. The sponsor's proposal for 25 mg & 100 mg tablets has been accepted through suitability petition (see page 6, vol.1.1).

4. No Patent or Exclusivity exists for the RLD.

5. The listing of inactive ingredients is accurate (see p.6346, vol.1.1)

6. The sponsor differentiated the strengths using different background color.

7. Storage/Dispensing Recommendations:

   NDA: Store at 25oC (77oF); excursions permitted to 15o - 30oC (59o - 86oF) (see USP Controlled Room Temperature)

   ANDA: Store at 25oC (77oF); excursions permitted to 15o - 30oC (59o - 86oF) (see USP Controlled Room Temperature
   See comment (a) under CONTAINER.

8. The 50 mg tablets for both ANDA and the RLD are scored. The 25 mg is not scored while the 100 mg is scored for the ANDA.

9. RLD is marketed in bottles of 30s & 100s. The firm proposes to market in bottles of 30s, 100s & 1000s for all strengths.

10. CONTAINER/CLOSURE

    Container - HPDE

    Closure - CRC and Non-CRC See comment (b) under CONTAINER and p.7643, vol.1.16

11. Mallinckrodt is the sole manufacturer (p.6565, vol.1.13).

12. The tablet description for the 100 mg is NOT accurate as listed in the HOW SUPPLIED section (p 7886, vol.1.16). See comment (ii) under H.S. section.

Date of Review: 12/20/01 Date of Submission: 10/31/01

Primary Reviewer: Chan Park C Park Date: 12/21/01

Team Leader: Charlie Hoppes Date: 12/21/01

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cc:

ANDA: 76-264
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-264** Date of Submission: **February 18, 2002**

Applicant's Name: **Mallinckrodt, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets USP, 25 mg, 50 mg, & 100 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 - 30s, 100s, & 1000s

Satisfactory in FPL as of 2/18/02 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 2/18/02 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes (25 mg & 100 mg)

What is the RLD on the 356(h) form: Re Via® (naltrexone HCL) tablets

NDA Number: 18-932/S-015

NDA Drug Name: Re Via® (naltrexone HCL) tablets

NDA Firm: DuPont Pharmaceutical Company

Date of Approval of NDA Insert and supplement #:
18-932/S-015; May 15, 2001

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: Innovator's labels

Post-Approval Revisions - INSERT:

Increase the prominence of the molecular formula under DESCRIPTION section.

Other Comments:

The sponsor's proposal for 25 mg & 100 mg tablets has been accepted through suitability petition

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FOR THE RECORD:

1. This review is based on the labeling for Revia® (DuPont, approved May 15, 2001). This is NDA 18-932/S-015.

2. This product is a subject of USP monograph.

3. The innovator has only 50 mg tablets approved. The sponsor's proposal for 25 mg & 100 mg tablets has been accepted through suitability petition (see page 6, vol.1.1).

4. No Patent or Exclusivity exists for the RLD.

5. The listing of inactive ingredients is accurate (see p.6346, vol.1.1)

6. The sponsor differentiated the strengths using different background color.

7. Storage/Dispensing Recommendations:

   NDA: Store at 25oC (77oF); excursions permitted to 15o - 30oC (59o - 86oF) (see USP Controlled Room Temperature)

   ANDA: Store at 25oC (77oF); excursions permitted to 15o - 30oC (59o - 86oF) (see USP Controlled Room Temperature

8. The 50 mg tablets for both ANDA and the RLD are scored. The 25 mg is not scored while the 100 mg is scored for the ANDA.

9. RLD is marketed in bottles of 30s & 100s. The firm proposes to market in bottles of 30s, 100s & 1000s for all strengths.

10. CONTAINER/CLOSURE

    Container - HPDE

    Closure - CRC and Non-CRC See p.7643, vol.1.16 See also attachment 1 of the 2/18/02 submission in which the sponsor indicated that the closure for the 30s is CRC (vol.3.1)

11. Mallinckrodt is the sole manufacturer (p.6565, vol.1.13).

12. The tablet description for all strengths is accurate as listed in the HOW SUPPLIED section. See p 7886, vol.1.16 and attachment 2 of the 2/18/02 submission (vol3.1).

Date of Review: 3/1/02 Date of Submission: 2/18/02

Primary Reviewer: Chan Park C Park Date: 3/1/02

Team Leader: Charlie Hoppes Date:

3/4/02

cc:

ANDA: 76-264
DUP/DIVISION FILE
HFD-613/CPark/CHoppes (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-264

3. NAME AND ADDRESS OF APPLICANT
Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Blvd
P.O. Box 5840
St. Louis, MO 63134

4. LEGAL BASIS FOR SUBMISSION
Proprietary Name: REVIA
NDA Holder: DUPONT MERCK
Strength: 50MG
NDA Number: 18-932
Approval Date: NOV 20, 1984
Reference Listed Drug: Yes

Patent and Exclusivity Certification: page 0015

There are no unexpired exclusivities or patents for this product.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Naltrexone Hydrochloride Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
31-OCT-2001: Original Submission
10-DEC-2001: New Correspondence
15-NOV-2001: New Correspondence
11-FEB-2002: Fax Amendment

FDA:
12-DEC-2001: Acknowledgement Letter
06-FEB-2002: T-Con

10. PHARMACOLOGICAL CATEGORY
Narcotic Antagonist

11. Rx or OTC
Rx

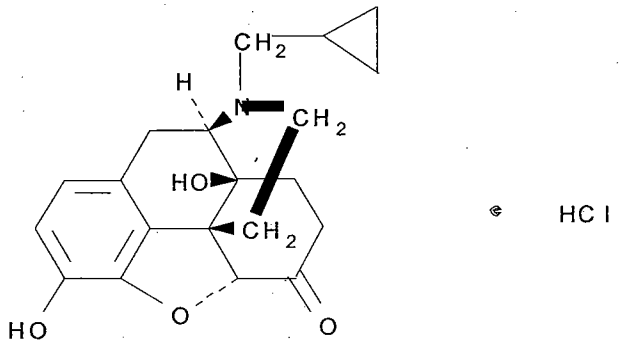
12. RELATED IND/NDA/DMF(s)
DMF #6265/Naltrexone Hydrochloride, USP/Mallinckrodt

13. DOSAGE FORM
Tablets

14. POTENCIES
25, 50, & 100 mg

15. CHEMICAL NAME AND STRUCTURE
$C_{20}H_{23}NO_4.HCl$; M.W. = 377.87

17(Cyclopropylmethyl)-4-5-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride.



16. RECORDS AND REPORTS
None

17. COMMENTS
API and Drug Product are compendial, MV not required
Bio Review is Satisfactory
Labeling Review is acceptable: 04-MAR-2002
EER is pending: 12-FEB-2002

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Approval pending EER.

19. REVIEWER:
D. Roselle, Ph.D.

DATE COMPLETED:
29-JAN-2002 (Fax: 12-FEB-2002)

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1 (pp 3-31)

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Not required, API and Drug Product are compendial.

32. LABELING
Labeling Review: Satisfactory 04-MAR-2002

33. ESTABLISHMENT INSPECTION
Pending: 12-FEB-2002

34. BIOEQUIVALENCY/MICROBIOLOGY STATUS
(MICROBIOLOGY - N/A)

Final Bio Review found satisfactory: 11-JAN-2002

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Categorical Exclusion request is provided on page 8374a.

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt? Yes SPOT? No

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confidential commercial

information from

Chemistry Review #1 (pp 33-34)

cc: ANDA 76-264
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/DCRoselle/2/12/02 D Roselle 3/6/02

HFD-640/GJSmith/2/12/02 3/6/02

HFD-618/JMin/2/25/02 3/15/02

F/T by rad/3/5/02

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TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

BIOEQUIVALENCE REVIEW(S)

12-11-01

2.1

Naltrexone Hydrochloride Tablets, USP
25 mg, 50 mg, and 100 mg
ANDA #76264
Reviewer: Carol Y. Kim
v:\firmsam\mallinckrodt\ltrs&rev\76254stf.O01

Mallinckrodt Inc.
Hazelwood, MO
Submission Date:
October 31, 2001

Review of two Bioequivalence Studies and Dissolution Data

I. Introduction

First Generic: Yes (New strengths)

Indication: Opioid antagonist

Contents of Submission:

- Fasting BE: 1 X 50 mg (test) vs. 1 X 50 mg (RLD)
- Fasting BE: 1 X 100 mg (test) vs. 2 X 50 mg (RLD)
- Waiver request: 25 mg
- *In vitro* dissolution data: 25 mg, 50 mg, and 100 mg

RLD: **ReVia**^{R} (naltrexone hydrochloride) Tablet, 50 mg, manufactured by Dupont Merck. (NDA# 018932, 11/20/84)

Recommended Dose: Starting with 25 mg/day, Target dose-50 mg/day

II. Pharmacokinetics

Naltrexone is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

Naltrexone is rapidly and almost completely (about 96%) absorbed following an oral administration, but the drug undergoes extensive first-pass metabolism in the liver. The major metabolite is 6-β-naltrexol. Like naltrexone, 6-β-naltrexol has opiate antagonist activity. Peak plasma concentrations of naltrexone and 6-β-naltrexol usually occur within 1 hour following oral administration of tablets. Plasma concentration of 6-β-naltrexol generally ranges 1.5-10 times greater than those of naltrexone. Naltrexone is 21-28% protein bound. Naltrexone and its metabolites (unconjugated and conjugated) are excreted principally in urine via glomerular filtration.

III. Background

1. In response to Lachman Consultant Services, Inc.'s suitability petition (docket no. 99P-4775/CP1), the Agency authorized a change in strength from that of the listed drug product (i.e., from 50 mg to 25 mg, 100 mg, and 150 mg) on April 13, 2000. The listed drug referred to in the petition is ReVia^{R}, 50 mg.

2. See below for the history of ANDA submissions.

Approved ANDAs			
ANDA	Approval dates	Firm's name	Comments
75-274	5/26/99	Amide	Fasting BE study only, 90 % CI applied on both parent and 6β-naltrexol
74-918	5/26/99	Barr	
75-434	3/8/00	Eon	
Unacceptable ANDA			
ANDA	Submission dates	Firm's name	Comments
[redacted]	[redacted]	[redacted]	-BE study is unacceptable due to reassay of one subject after completion of the study.
Protocols			
ANDA	DBE acceptance dates	Firm's name	Comments
[redacted]	[redacted]	[redacted]	Protocols are acceptable

IV. Protocol No. 0119-01-727: Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Mallinckrodt, Inc.'s Naltrexone Tablets, 100 mg (1 X 100 mg), and DuPont Pharma Company's ReVia^{R} Tablets, 50 mg (2 X 50 mg), in Healthy Volunteers Under Fasting Conditions

Study information

Clinical Facility: [redacted]

Principal Investigator: [redacted] D.O.

Clinical Study Dates: Period I: 3/9-11/01
Period II: 3/16-18/01

Dosing dates:	(I)	(II)
Group 1 (#1-25):	3/10/01	3/17/01
Group 2 (#26-50):	3/11/01	3/18/01

Analytical Facility: [redacted]

Analytical Director: [redacted]

Analytical Study Dates: 4/7/01-4/23/01

Storage Period: No > 51 days at -20°C

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Naltrexone Tablet	ReVia[R] Tablet
Manufacturer:	Mallinckrodt, Inc.	DuPont Pharma Company
Manufacture Date:	2/8/01	N/A
Expiration Date:	-	4/02
ANDA Batch Size:	[redacted]	-
Full Batch Size:	[redacted]	-
Batch/Lot Number:	MHSC 0110	PD350B
Strength:	100 mg	50 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1 Tablet	2 Tablets (2 X 50 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours fasting pre-dosing 4 hours post-dosing	10 hours fasting pre-dosing 4 hours post-dosing

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	1 week
No. of Treatments:	2	**Center**	single

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 Randomized:**	50
Route of Administration:	oral	**No. of Subjects Enrolled:**	50
		No. of Subjects Completing:	47
		No. of Subjects Plasma Analyzed:	47
		No. of Dropouts:	3
		Sex(es) Included:	33 males + 14 females
		Age:	18-64 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	49

Inclusion/Exclusion Criteria:	Vol. 1.3, pp. 953-957
Housing:	Approximately 12 hours before dosing until after the 24 hours sampling in each period
Blood Sampling:	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12, 16, 24, 36, 48,

	60, and 72 hours post dose
Volume:	10 ml

Study Results

1) Clinical

Demographic Data (all completed patients)

Subj	Race			Sex		Age Group (Yr.)			Height (in)		Weight (lbs.)	
Total	Black	Caucasian	other	Male	Female	mean	18-40	41-65	Mean	Range	Mean	Range
47	1	45	1	33	14	29	36	11	70	62-75	167	118-230

Adverse Events: -Total- 49 adverse events in association to the study drug
-26 events (17 subjects)-treatment A related
-23 events (9 subjects)-treatment B related
-The adverse events were mild headache and nausea. (vol. 1.3, p. 941-942)

Vomiting Episodes:

Subjects	Treatment	Date	Time at vomiting	Time Dosed	Comments
13	B	3/12/01	2100	0612	Vomiting occurred after 2 X median Tmax (0.75 hour)
17	B	3/10/01	1316	0616	Vomiting occurred after 2 X median Tmax (3.0 hour)
17	A	3/17/01	0740	0615	Vomiting occurred within 2 X median Tmax (1.00 hour)
23	B	3/10/01	0850	0622	Vomiting occurred within 2 X median Tmax (1.25 hour)

Therefore, subjects #17 and #23 should be dropped from the final analysis.

Dropouts:

Subjects	Reasons	Exclusion from the final analysis
Subjects #13 and #15	Did not return for period I (72 hour blood draw) and for period II	Yes
Subject #35	Dropped due to adverse event (vomiting) in period I prior to 72 hour blood draw and vital signs	Yes

Protocol Deviations:

-Minor deviations were noted.

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation (data from third amendment report):

ANALYTE:	Naltrexone	6β-naltrexol
ASSAY METHOD:	LC/MS/MS	LC/MS/MS
INTERNAL STANDARD	naloxone	
MATRIX:	Human EDTA Plasma	Human EDTA Plasma
LOQ:	0.2 ng/ml	1.0 ng/ml
STANDARD CURVE HIGHEST CONC.:	100 ng/ml	500 ng/ml
STANDARD CURVE LOWEST CONC.:	0.2 ng/ml	1.0 ng/ml
R**2 =	0.9989	0.9981
SPECIFICITY:	No interference noted	No interference noted
ANALYTE RETENTION TIME:	1.22 min.	2.07 min.
QC SAMPLES	0.6 ng/ml 37.5 ng/ml 75.0 ng/ml	3.0 ng/ml 188 ng/ml 375 ng/ml
PRECISION (QC):	2.4-7.2% CV within day	4.0-5.8% CV within day
ACCURACY (QC):	96.0-101 % of nominal value within day	95.1-106 % of nominal value within day
STABILITY: Bench top: Extract stability: Frozen in plasma at -20°C: Freeze-thaw:	 8 hours at RT 73 hours at RT 30.5 weeks 5 cycles	
Data from first pre-validation study report		
QC SAMPLES: PRECISION (QC): ACCURACY (QC):	0.6 ng/ml 8.0 ng/ml 16 ng/ml 3.1-7.7 % CV between day 101.3-105.7% of nominal value between day	6.0 ng/ml 80.0 ng/ml 160 ng/ml 5.4-8.6% CV between day 101.6-103.5% of nominal value between day
RECOVERY:	0.2 ng/ml: 91.8 % 2.0 ng/ml: 93.6 % 20.0 ng/ml: 95.2 %	2.0 ng/ml: 99.6 % 20.0 ng/ml: 88.4 % 200 ng/ml: 93.0 %
RECOVERY OF INTERNAL STANDARD:	86.8%	

During Assay Validation

ANALYTE:	Naltrexone	6β-naltrexol
ASSAY METHOD:	LC/MS/MS	LC/MS/MS
MATRIX:	Human EDTA Plasma	Human EDTA Plasma
LOQ:	0.2 ng/ml	1.0 ng/ml
STANDARD CURVE HIGHEST CONC.:	100 ng/ml	500 ng/ml
STANDARD CURVE LOWEST CONC.:	0.2 ng/ml	1.0 ng/ml
R**2 MEAN:	0.9966	0.9980
QC SAMPLES	0.6 ng/ml 37.5 ng/ml 75.0 ng/ml	3.0 ng/ml 188 ng/ml 375 ng/ml
PRECISION (QC):	5.2-12.4% CV between day	5.6-8.4% CV between day
ACCURACY (QC):	92.1-95.5% of nominal between day	96.1-101% of nominal between day

Reassays: A total of 2030 samples were assayed. None were repeated for PK reasons.

Conclusion: The analytical method validation report is complete.

3) Pharmacokinetic/Statistical Analysis

Mean Naltrexone and 6-β-naltrexol plasma levels are summarized in Table 1.

Table 1: Mean Naltrexone and 6-β-naltrexol Plasma Concentrations following an oral dose of 100 mg for test (1 X 100 mg) and reference (2 X 50 gm) products

Sampling	Naltrexone : Test Lot# MHSC 0110		Naltrexone: Reference Lot # PD350B		Ratio	6-β-naltrexol: Test Lot# MHSC 0110		6-β-naltrexol: Reference Lot# PD350B		Ratio
Time (hour)	Mean (ng/ml)	STD	Mean (ng/ml)	STD	T/R	Mean (ng/ml)	STD	Mean (ng/ml)	STD	T/R
0	-	-	-	-	-	-	-	-	-	-
0.25	1.06	0.960	1.25	1.284	0.85	17.66	19.436	16.02	19.409	1.10
0.5	9.25	7.908	8.58	6.037	1.08	123.16	96.326	107.47	64.414	1.15
0.75	15.07	12.306	13.32	8.016	1.13	170.56	97.058	153.77	82.857	1.11
1	15.72	12.638	13.62	7.453	1.15	161.58	85.650	157.98	71.994	1.02
1.25	14.21	11.431	13.75	7.722	1.03	146.78	72.067	153.39	60.547	0.96
1.5	13.02	9.412	13.29	7.904	0.98	137.54	62.665	147.21	60.420	0.93
2	12.50	10.116	12.44	8.543	1.00	132.98	53.847	136.68	45.534	0.97
2.5	11.38	8.812	11.48	7.908	0.99	127.30	37.344	131.93	40.673	0.96
3	9.57	6.440	9.61	6.504	1.00	118.49	31.890	118.99	36.911	1.00
4	6.77	4.355	6.76	4.324	1.00	99.03	26.286	98.97	29.150	1.00
5	4.80	3.020	4.97	3.628	0.97	90.16	21.383	90.58	25.434	1.00
7	2.50	1.789	2.88	3.178	0.87	68.41	14.981	72.82	24.948	0.94
9	1.30	0.98	1.48	1.941	0.88	52.05	12.303	54.91	22.039	0.95
12	0.82	0.559	0.88	0.827	0.93	41.68	10.731	42.96	13.364	0.97
16	0.51	0.439	0.50	0.614	1.02	32.45	8.514	32.17	9.901	1.01
24	0.47	0.352	0.47	0.334	1.00	23.37	5.989	23.20	7.253	1.01
36	0.60	0.531	0.33	0.044	1.82	12.34	3.810	12.01	4.391	1.03
48	0.22	0.004	-	-	-	6.54	2.386	6.62	2.985	0.99
60	-	-	-	-	-	3.71	1.566	3.86	1.919	0.96
72	-	-	-	-	-	2.32	0.972	2.36	1.201	0.98

In this study, the subjects were randomized into two groups of 25 subjects each for dosing on different dates. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean pharmacokinetic parameters for naltrexone and 6-β-naltrexol are shown in Table 2. The LS means of the log-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2: Test mean/Reference mean ratios of Naltrexone and 6-β-naltrexol pharmacokinetic parameters (n=47)

	Naltrexone					6-β-naltrexol				
Parameter*	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]
AUCT	65.94	71.03	64.10	59.15	1.03	1762.49	22.56	1784.62	24.79	0.99
AUCI	69.20	70.13	65.71	58.15	1.05	1813.97	22.85	1834.36	25.38	0.99
CMAX	19.11	66.10	17.80	50.67	1.07	209.35	34.95	205.11	30.86	1.02
TMAX	1.41	65.47	1.46	59.31	0.97	1.24	62.75	1.42	59.20	0.87
T ½	4.23	98.58	3.33	33.46	1.27	13.91	15.77	14.07	16.38	0.99
KE	0.20	30.47	0.23	30.43	0.87	0.05	15.54	0.05	15.85	1.00

*AUCT=ng*hr/ml, AUCI=ng*hr/ml, TMAX=hr, CMAX=ng/ml
[1]Calculated by reviewer

Table 3: Geometric Mean ratios and 90% confidence intervals for naltrexone and 6-β-naltrexol (n=47)

Naltrexone

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-t	56.56	56.24	1.0	95.32	106.1
LAUC0-inf	59.31	57.98	1.0	96.22	108.7
LCmax	16.34	15.84	1.0	94.83	112.2

6-β-naltrexol

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-t	1719.60	1731.48	0.99	97.22	101.5
LAUC0-inf	1768.85	1777.44	0.99	97.41	101.7
LCmax	198.16	195.91	1.01	94.35	108.4

*LAUC0-inf =ng*hr/ml, LAUC0-t=ng*hr/ml, LCMAX=ng/ml

Comments:

1. Subjects # 17 and 23 vomited within 2X median Tmax. Therefore these two subjects should be deleted from the final analysis. The 90% CI excluding these subjects do not change the outcome of the study. (Naltrexone: LAUCT=94.43-104.9; LAUCI=95.32-107.9;LCMAX=93.59-111.5, 6-β-naltrexol: : LAUCT=97.91-101.7; LAUCI=98.19-101.7;LCMAX=93.87-108.6)

2. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were slightly different with the values determined by the firm. The firm did not exclude dropout subjects (#13, 17 and #35) in the final analysis. However, the 90% CI excluding dropouts did not change the outcome of the study.

3. The mean (%CV) AUC_T/AUC_I ratios of naltrexone were 0.96 (6.67), range 0.57 to 0.99, and 0.97 (2.13), range 0.89 to 0.99, for test and reference, respectively. The mean (%CV) AUC_T/AUC_I ratios of 6-β-naltrexol were 0.97 (1.6), range 0.91 to 0.99, and 0.97 (1.3), range 0.94 to 0.99, for test and reference, respectively.

4. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX for naltrexone and 6-β-naltrexol are all within 80-125% range.

Conclusion: The study is acceptable.

V. Protocol No. 0092-01-729:Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Mallinckrodt, Inc.'s Naltrexone Tablets, 50 mg (1 X 50 mg), and DuPont Pharma Company's ReVia[R] Tablets, 50 mg (1 X 50 mg), in Healthy Volunteers Under Fasting Conditions

Study information

Clinical Facility:	———————		
	———		
Principal Investigator:	———, M.D.		
Clinical Study Dates:	Period I: 3/10-17/01		
	Period II: 3/17-24/01		
	Dosing dates:	(I)	(II)
	Group 1 (#1-25):	3/10/01	3/17/01
	Group 2 (#26-50):	3/17/01	3/24/01
Analytical Facility:	———————		
	———		
Analytical Director:	———————		
Analytical Study Dates:	4/19/01-5/3/01		
Storage Period:	No > 54 days at -20°C		

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Naltrexone Tablet	ReVia[R] Tablet
Manufacturer:	Mallinckrodt, Inc.	DuPont Pharma Company
Manufacture Date:	2/13/01	N/A
Expiration Date:	-	4/02
ANDA Batch Size:	[redacted]	-
Full Batch Size:	[redacted]	-
Batch/Lot Number:	MHSC 0109	PD350B
Strength:	50 mg	50 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1 Tablet	1 Tablet
Study Condition:	Fasting	Fasting
Length of Fasting:	overnight fasting pre-dosing hours post-dosing	overnight fasting pre-dosing hours post-dosing

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	1 week
No. of Treatments:	2	**Center**	Single

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 Randomized:**	50
Route of Administration:	Oral	**No. of Subjects Enrolled:**	50
		No. of Subjects Completing:	49
		No. of Subjects Plasma Analyzed:	49
		No. of Dropouts:	1
		Sex(es) Included:	9 males + 40 females
		Age:	19-75 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	73

Inclusion/Exclusion Criteria:	Vol. 1.8, pp. 3676-3680
Housing:	The night before dosing until after the 24 hours sampling in each period
Blood Sampling:	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12, 16, 24, 36, 48, 60, and 72 hours post dose
Volume:	10 ml

Study Results

1) Clinical

Demographic Data (all randomized patients)

Subj	Race			Sex		Age Group (Yr.)				Height (in)		Weight (lbs.)	
Total	Black	Caucasian	other	Male	Female	mean	18-40	41-65	66-75	Mean	Range	Mean	Range
50	3	47	0	10	40	45	17	29	4	65	59-72	143	99.3-201

Adverse Events: -Total- 73 adverse events in association to the study drug
-37 events (18 subjects)-treatment A related
-36 events (19 subjects)-treatment B related
-The adverse events were mild to moderate lightheadedness and drowsiness. (vol. 1.8, p. 3543-3547)

Dropout:

Subjects #13	Withdrew consent and did not return for period II

Protocol Deviations:
-Minor deviations were noted.

2) Analytical (Not to be Released Under FOI)

During Assay Validation

ANALYTE:	Naltrexone	6β-naltrexol
ASSAY METHOD:	LC/MS/MS	LC/MS/MS
MATRIX:	Human EDTA Plasma	Human EDTA Plasma
LOQ:	0.2 ng/ml	1.0 ng/ml
STANDARD CURVE HIGHEST CONC.:	100 ng/ml	500 ng/ml
STANDARD CURVE LOWEST CONC.:	0.2 ng/ml	1.0 ng/ml
R**2 MEAN:	0.9963	0.9970
QC SAMPLES	0.6 ng/ml 37.5 ng/ml 75.0 ng/ml	3.0 ng/ml 188 ng/ml 375 ng/ml
PRECISION (QC):	5.4-16.6% CV between day	5.9-23.0% CV between day
ACCURACY (QC):	92.3-94.0% of nominal between day	95.2-98.5% of nominal between day

Reassays: A total of 2079 samples were assayed. None were repeated for PK reasons.

Conclusion: The analytical method validation report is complete.

3) Pharmacokinetic/Statistical Analysis

Mean Naltrexone and 6-β-naltrexol plasma levels are summarized in Table 1.

Table 1: Mean Naltrexone and 6-β-naltrexol Plasma Concentrations following an oral dose of 100 mg for test (1 X 50 mg) and reference (1 X 50 mg) products

Sampling	Naltrexone : Test Lot# MHSC 0109		Naltrexone: Reference Lot # PD350B		Ratio	6-β-naltrexol: Test Lot# MHSC 0109		6-β-naltrexol: Reference Lot# PD350B		Ratio
Time (hour)	Mean (ng/ml)	STD	Mean (ng/ml)	STD	T/R	Mean (ng/ml)	STD	Mean (ng/ml)	STD	T/R
0	-	-	-	-	-	-	-	-	-	-
0.25	1.09	1.428	0.81	0.676	1.35	12.98	14.501	9.08	8.465	1.43
0.5	4.75	3.695	3.76	2.675	1.26	64.97	38.741	54.77	37.084	1.19
0.75	7.62	4.090	6.42	4.022	1.19	93.17	43.674	84.07	44.861	1.11
1	7.97	3.918	7.20	4.048	1.11	94.35	36.948	89.68	38.861	1.05
1.25	7.49	3.934	7.21	3.965	1.04	86.93	32.656	88.17	37.218	0.99
1.5	6.99	3.763	6.55	3.866	1.07	84.97	29.184	83.73	35.000	1.01
2	5.75	3.017	5.47	2.899	1.05	78.29	23.332	78.87	31.099	0.99
2.5	4.64	2.342	4.55	2.283	1.02	72.56	21.251	72.43	24.202	1.00
3	3.74	1.932	3.69	1.911	1.01	64.83	16.468	65.88	21.300	0.98
4	2.44	1.225	2.38	1.242	1.03	54.45	14.986	54.92	16.728	0.99
5	1.62	1.036	1.73	1.133	0.94	46.21	12.165	49.94	15.677	0.93
7	0.91	0.647	0.89	0.637	1.02	36.19	9.398	37.07	11.689	0.98
9	0.61	0.464	0.60	0.419	1.02	28.60	8.717	28.91	9.973	0.99
12	0.47	0.249	0.54	0.391	0.87	23.35	7.144	23.74	7.636	0.98
16	0.35	0.143	0.42	0.167	0.83	19.00	5.253	19.51	6.666	0.97
24	0.36	-	-	-	-	12.87	3.993	12.96	4.283	0.99
36	-	-	-	-	-	6.48	2.492	6.74	2.652	0.96
48	-	-	-	-	-	3.79	1.632	3.94	2.110	0.96
60	-	-	-	-	-	2.28	1.031	2.52	1.411	0.90
72	-	-	-	-	-	1.78	0.659	1.89	1.042	0.94

Study subjects were randomized into two groups of 25 subjects each for dosing. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for naltrexone and 6-β-naltrexol are shown in Table 2. The LS means of the log-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2: Test mean/Reference mean ratios of Naltrexone and 6-β-naltrexol pharmacokinetic parameters (n=49)

	Naltrexone					6-β-naltrexol				
Parameter*	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]
AUCT	27.32	53.14	25.96	51.32	1.05	991.00	27.21	996.34	31.57	0.99
AUCI	29.16	51.99	28.53	50.46	1.02	1026.81	27.08	1035.90	31.85	0.99
CMAX	8.73	48.65	8.23	50.21	1.06	109.38	34.01	105.63	35.36	1.04
TMAX	1.08	44.10	1.32	59.46	0.82	1.26	53.72	1.48	62.45	0.85
T ½	3.91	52.46	4.71	95.16	0.83	14.07	22.30	13.94	22.14	1.01
KE	0.23	56.85	0.22	52.91	1.05	0.05	18.94	0.05	21.05	1.00

*AUCT=ng*hr/ml, 17.63AUCI=Ng*hr/ml, TMAX=hr, CMAX=ng/ml

[1]Calculated by reviewer

Table 3: Geometric Mean ratios and 90% confidence intervals for naltrexone and 6-β-naltrexol (n=49)

Naltrexone

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-t	23.71	23.01	1.03	98.00	108.34
LAUC0-inf	25.47	25.26	1.00	95.98	105.92
LCmax	7.74	7.32	1.06	98.76	113.27

6-β-naltrexol

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-t	957.60	952.28	1.00	96.97	104.28
LAUC0-inf	992.88	990.48	1.00	96.74	103.87
LCmax	103.88	99.20	1.05	98.69	111.10

*LAUC0-inf =ng*hr/ml, LAUC0-t=ng*hr/ml, LCMAX=ng/ml

Table 4: Root Mean Square Error (MSE) for ln-transformed AUCT and Cmax

	naltrexone		6-β-naltrexol	
MSE, Test & Reference	ln AUCT	ln CMAX	ln AUCT	ln CMAX
Fasting (1 X 100 mg vs. 2 X 50 mg)	0.1542766	0.2428814	0.0615715	0.2007207
Fasting (1 X 50 mg vs. 1 X 50 mg)	0.1478282	0.1454487	0.1071277	0.1748140

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were in good agreement with the values determined by the firm.

2. The mean (%CV) AUC_T/AUC_I ratios of Naltrexone were 0.93 (4.17), range 0.77 to 0.98, and 0.91 (6.67), range 0.67 to 0.97, for test and reference, respectively. The mean (%CV) AUC_T/AUC_I ratios of 6-β-naltrexol were 0.96 (1.6), range 0.90 to 0.98, and 0.96 (2.2), range 0.90 to 0.98, for test and reference, respectively.

3. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX for naltrexone and 6-β-naltrexol are all within 80-125% range.

Conclusion: The study is acceptable.

VI. Dissolution

The firm submitted dissolution data for Naltrexone Tablets, 25 mg, 50 mg, and 100 mg, obtained using the USP method.

Method of dissolution	USP 24, Apparatus II (paddles)
Speed	50 rpm
No. of Units Tested	12
Medium	Water
Temperature	37°C
Volume	900 ml
Specifications	NLT 80% (Q) is dissolved in 60 minutes
Assay Methodology	HPLC method
Reference Product	Du Pont Pharma's ReVia^R Tablet, 50 mg

Result of In Vitro Dissolution Profile Summary for Naltrexone 50 mg

Sampling Times (minutes)	Test Lot # MHSC 0109 **Strength: 50 mg**			ReVia^R Lot # PD350B **Strength: 50 mg**		
	Mean %	Range %	%CV	Mean %	Range %	%CV
15	78.8	68.2-93.6	7.0	57.4	47.8-66.6	4.5
30	93.9	91.0-97.6	2.4	88.0	82.0-92.4	3.4
45	96.8	94.4-101.2	2.1	95.7	92.8-100.6	1.9
60	96.6	94.2-100.6	1.6	97.9	94.4-102.4	2.4

Sampling Times (minutes)	Test Lot # MHSC 0108 **Strength: 25 mg**			Test Lot # MHSC 0110 **Strength: 100 mg**			ReVia^R Lot # PD350B **Strength: 50 mg**		
	Mean %	Range %	%CV	Mean %	Range %	%CV	Mean %	Range %	%CV
15	91.6	84-101.2	5.1	64.1	53.0-74.7	7.3	57.4	47.8-66.6	4.5
30	98.9	92.8-105.2	3.2	94.6	85.8-101.3	5.2	88.0	82.0-92.4	3.4
45	97.6	93.2-103.2	3.1	97.9	92.6-102.6	3.0	95.7	92.8-100.6	1.9
60	99.3	94.4-103.2	2.4	98.5	96.0-101.0	1.7	97.9	94.4-102.4	2.4

Dissolution testing site: not specified

Similarity factors (f_2) for naltrexone:

	f_2
Test 50 mg vs. Test 100 mg	56

Comments

The firm conducted dissolution according to the procedure recommendation by the USP method. The dissolution rate for the 25-mg tablet was more rapid than for the 50- and 100-mg strengths. The 25-mg strength averaged 92% dissolved in 15 minutes. At 15 minutes, the 50- and 100-mg strengths averaged 79% and 64% dissolved, respectively. However, at 30 minutes, the 25-mg strength averaged 98% dissolved and the other two strengths averaged 94-95% dissolved. Since naltrexone Tmax is about 1 to 1.5 hr, and the amount dissolved is comparable at 30 minutes for all three strengths,

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of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW (P. 14)

Assay and Content Uniformity

Product	Assay %	Content Uniformity(%RSD)
Test, Naltrexone Tablets, 50 mg Lot # MHSC0109	98.0	99.3 (1.3)
Reference, ReVia^{R} Tablets, 50mg Lot # PD350B	96.3	99.9 (2.3)
Test, Naltrexone Tablets, 100 mg Lot # MHSC0110	97.8	101.2 (1.6)

VIII. Waiver Request

1. The firm requested a waiver of *in vivo* bioequivalence testing for the 25 mg tablets.

2. The formulation of Naltrexone Tablets, 25 mg, is proportionally similar to the 50 mg and 100 mg strengths of the test products which underwent acceptable *in vivo* bioequivalence testing.

IX. Recommendations

1. The single-dose bioequivalence study, 0119-01-727, under fasting conditions, conducted by Mallinckrodt Inc., on its Naltrexone Hydrochloride Tablets, USP, 100 mg, #MHSC0110, comparing it to ReVita^{R} Tablets, 50 mg, #PD350B, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mallinckrodt Inc.'s Naltrexone Hydrochloride Tablet, USP, 100 mg, is bioequivalent to the reference product, ReVia^{R} Tablet, 50 mg, manufactured by DuPont Pharma Company.

2. The single-dose bioequivalence study, 0092-01-729, under fasting conditions, conducted by Mallinckrodt Inc., on its Naltrexone Hydrochloride Tablets, USP, 50 mg, #MHSC0109, comparing it to ReVita^{R} Tablets, 50 mg, #PD350B, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mallinckrodt Inc.'s Naltrexone Hydrochloride Tablet, USP, 50 mg, is bioequivalent to the reference product, ReVia^{R} Tablet, 50 mg, manufactured by DuPont Pharma Company.

3. The dissolution method conducted by Mallinckrodt Inc. on its Naltrexone Hydrochloride Tablets, 25 mg (lot #MHSC0108), 50 mg (lot #MHSC0109), and 100 mg (lot #MHSC0110) 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 water at 37°C using USP 24 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

5. The waiver of *in vivo* bioequivalence study requirements for the 25 mg tablet of the test product is granted. The formulation of Naltrexone Hydrochloride Tablet, USP, 25 mg is proportionally similar to the 50 mg and 100 mg strengths of test products which underwent acceptable *in vivo* bioequivalence testing. The Division of Bioequivalence deems Naltrexone Hydrochloride Tablets, USP, 25 mg, manufactured by Mallinckrodt Inc., to be bioequivalent to ReVia^{R} Tablets, 50 mg, manufactured by DuPont Pharma Company.

The firm should be informed of the above recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

For RD INITIALLED BY BDAVIT Manali Gokhale Date: 1/11/02
FT INITIALLED BY BDAVIT

Concur: for Dale P. Conner, Pharm.D. Date: 1/11/02
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76264 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Naltrexone Hydrochloride Tablets, USP, 25 mg, 50 mg, and 100 mg

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as per USP.

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 Barbara Myers Davis

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

CC: ANDA #76264
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim CK 1/11/02
For HFD-658/ Bio team Leader B. Davit Manali Gokhale 1/11/02
HFD-650/ S. Mazzella
for HFD-650/ D. Conner BWD 1/11/02

BIOEQUIVALENCY - ACCEPTABLE Submission date:10/31/01

ok **1. Fasting Study (STF)** **Strength: 50 mg**
Clinical: [redacted]
Analytical: [redacted] **Outcome: AC**

ok **2. Fasting Study (STF)** **Strength: 100 mg**
Clinical: [redacted]
ok Analytical: [redacted] **Outcome: AC**

3. DISSOLUTION WAIVER (DIW) **Strength: 25 mg**

Outcome: AC

4. New Correspondence (NC)
(12/21/01; diskettes)

Outcome Decisions: **AC** - Acceptable

WinBio Comments: Fasting Studies -Acceptable
Dissolution -Acceptable

Fig. 1: Mean plasma concentrations of naltrexone (Study 727), 100 mg test vs. 2 X 50 mg Ref, ANDA #76264

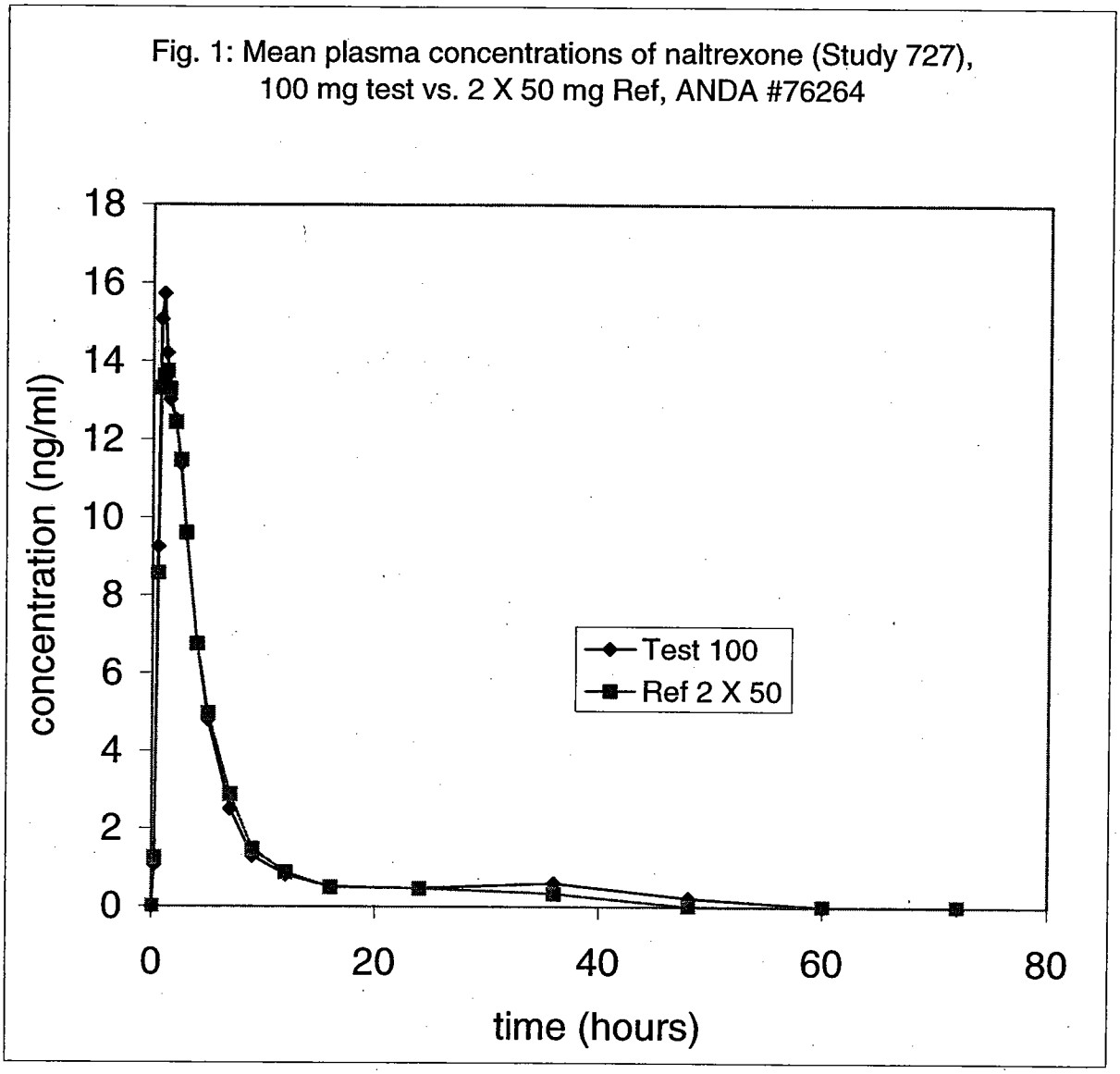


Fig. 2: Mean plasma concentrations of 6B-naltrexol (study 727), 100 mg test vs. 2 X 50 mg Ref, ANDA # 76264

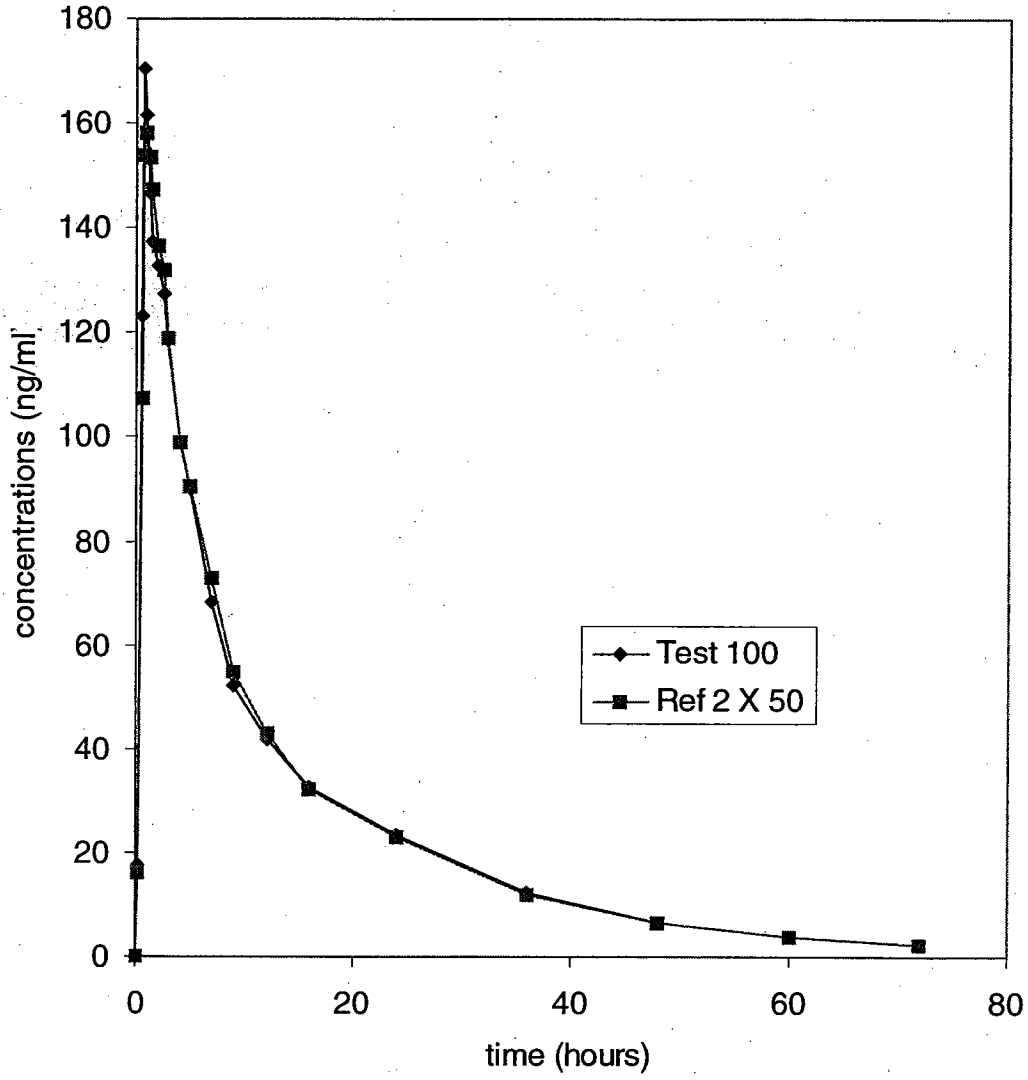


Fig. 3: Mean plasma concentrations of naltrexone (study 729),Test 50 mg vs. Ref 50 mg, ANDA #76264

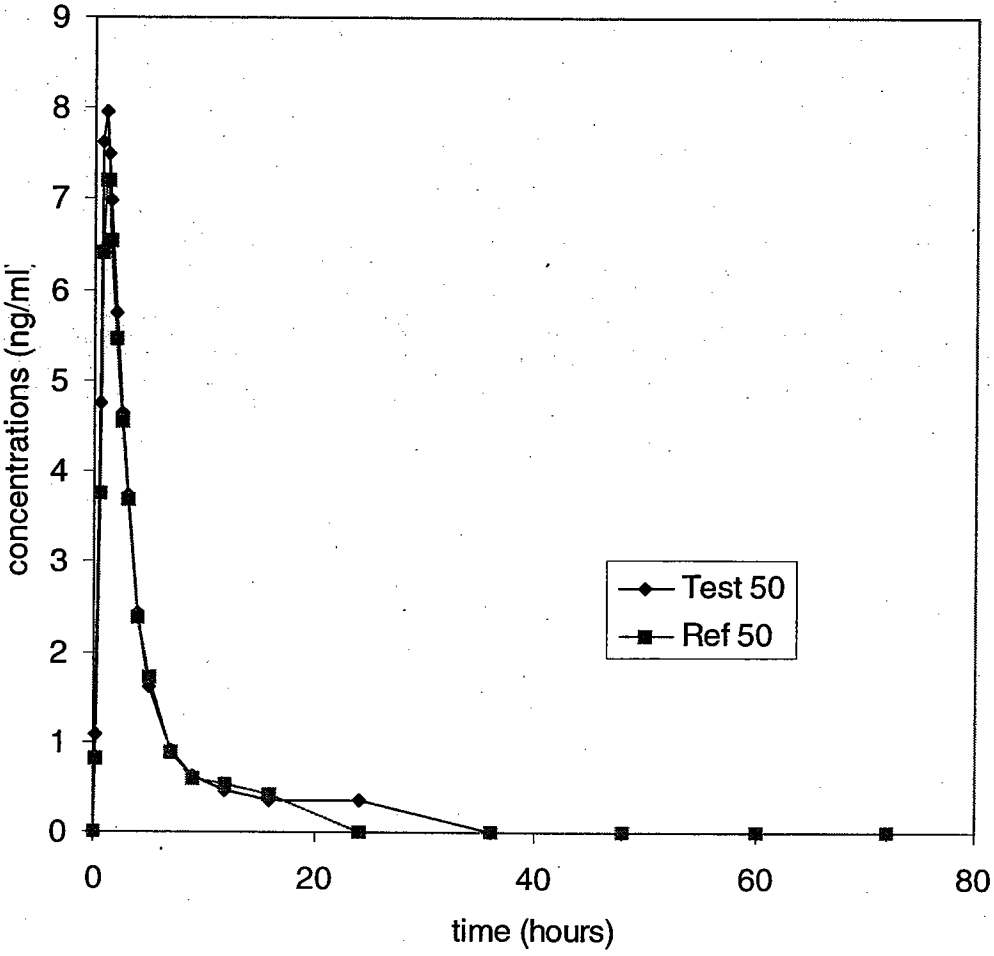


Fig. 4: Mean plasma concentrations of 6B-naltrexol (study 729), Test 50 mg vs. Ref 50 mg, ANDA #76264

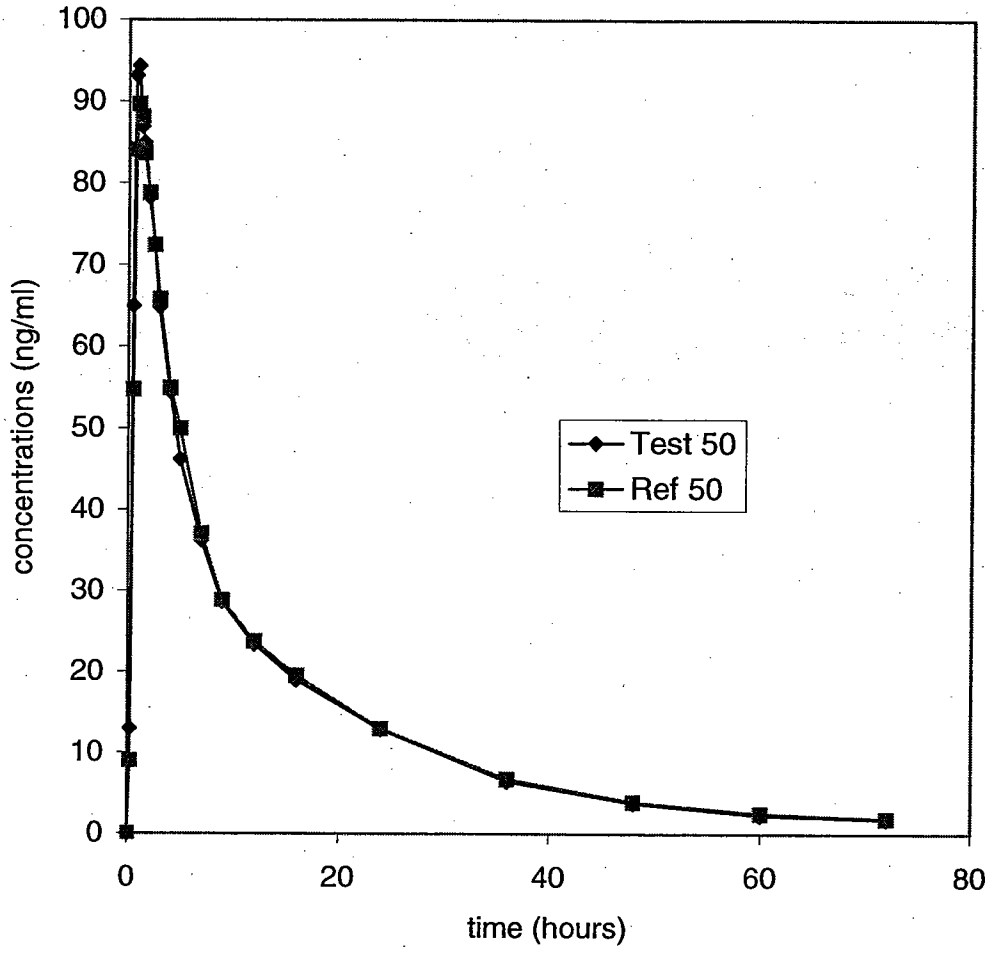
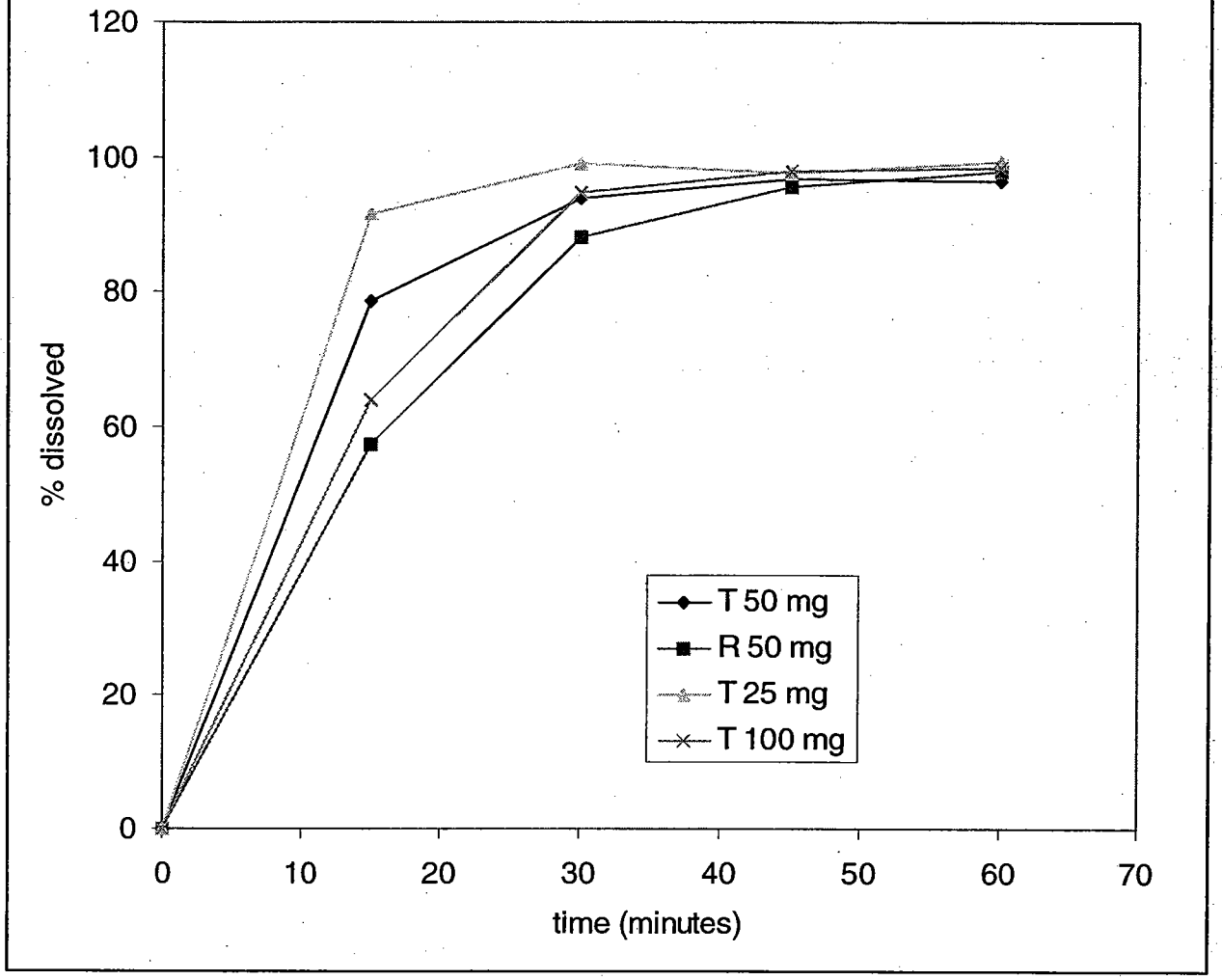


Fig. 5: Dissolution profile comparison, ANDA# 76264



OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-264 SPONSOR :Mallinckrodt, Inc.

DRUG AND DOSAGE FORM : Naltrexone Hydrochloride Tablets, 25 mg, 50 mg and 100 mg

STRENGTH(S) : 25 mg, 50 mg and 100 mg

TYPES OF STUDIES : STF X STP STM OTHER X

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY: In single-dose fasting BE studies, Naltrexone HCl Tablets, 50 mg and 100 mg, were shown to be bioequivalent to ReVia[R] Tablets, 50 mg. A waiver for the 25 mg strength is granted.

Formulation is acceptable.

DISSOLUTION : acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : Cel Y. K DATE : 1/11/02

TEAM LEADER : For Barbara M. Davit BRANCH : 3

INITIAL : MSK DATE : 1/11/02

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : B MD DATE : 1/11/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : November 7, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) Davis 08-NOV-2001

SUBJECT: Examination of the request for a bioequivalence study and waiver submitted with an ANDA for Naltrexone Hydrochloride Tablets USP, 50 mg **(the 25 mg and 100 mg are new strengths per suitability petition)** to determine if the application is substantially complete for filing.

Mallinckrodt Inc. Submitted ANDA 76-264 for Naltreone Hydrochloride Tablets USP, 50 mg **(the 25 mg and 100 mg are new strength per suitability petition)**. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for a bioequivalence study and waiver submitted by Mallinckrodt on October 31, 2001 for its Naltrexone Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

✓ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

concur: Barbara McDowell 11/9/01

John P. Skelly 11/14/01

Director, Division of Bioequivalence Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-264 DRUG NAME Naltrexone HCl Tablets USP FIRM Mallinckrodt Inc.

DOSAGE FORM(s) tablet 25mg, 50mg and 100mg

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms					
Consent forms	✓				
Composition	✓				individual quantitative composition of the coding (— Beige, Yellow + pink —) is nee
Summary of study	✓				
Individual Data & Graphs, ~~Linear~~ & Ln	✓				individual data graph only in semi-log scale submitted for all studies.
PK/PD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				
Assay of active content drug	✓				APPEARS THIS WAY ON ORIGINAL
Content uniformity	✓				
Date of manufacture (test products)		✓			It's unclear which date is refering to manufacture date according to ex-white book recived in Red Jacket Vol. 1.2-1.4.
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	✓				25mg strength tablet only for a change in strength (50mg to 25mg 100mg

Final Jacket Sent 12/04

Additional comments: Based on the approved citizen petition #1 99P-4775/CP1 (Approved on April 13, 2000), the firm submitted one pilot (P#0119-00-606) and two pivotal BE studies (Study# 727 and #729) under fasting conditions. The study #727 is conducted with 2x 50mg (RLD) vs. 1x100mg (test). Study#729 is conducted with 1x50mg (RLD) vs. 1x50mg (test). Although the CP was approved for 25mg, 100mg and 150mg strength tablets, the firm is not seeking approval for the 150mg strength tablet at this time.

TN BBE currently requests only fasting BE on Naltrexone tablets. (Control # ———)

Concur,
Barbara M Davis
11/9/01

Recommendation: ~~COMPLETE~~ / INCOMPLETE

Please note that the firm only submitted individual plasma graphs in semi-log scale. The reviewer needs to see the linear graph also. Individual quantitative comparisons of the coatings (—— Beige, yellow and pink ——) should be submitted for the review. Date of Manufacture for the test products, 25mg, Reviewed by 50mg, and 100mg, should be submitted.

11/9/01

_____ Date _____

Revised 6/7/2000

Dale was uncomfortable stating that the bio information submitted was incomplete but still met statutory requirements for filing. Therefore, the bio section will be considered "complete" but Reg. Support will still ask for the requested information within the text of the filing review.

Davis
21-NOV-2001

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-264 Applicant Mallinckrodt
Drug Naltrexone Tablet Strength 25mg, 50mg, 100mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
1. Project Manager Jeen Min Review Support Branch 9	Date 2/25/02 Initials JM	Date 9/18/02 Initials JM

Application Summary:

Original Rec'd date 10/31/01
Date Acceptable for Filing 11/6/01 ✓
Patent Certification (type) II
Date Patent/Exclus.expires N/A
Citizens Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
(If YES, check PETS)
Pediatric Exclusivity Tracking System (PETS)
Date checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status
Date of Office Bio Review 1/11/02
Date of Labeling Approv. Sum 3/4/02
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
30 Day Clock Start End
Commitment Rcd. from Firm Yes ☐ No ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

2. Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:	Date 3/18/02 Initials	Date 3/19/02 Initials

CMC Satisfactory, EER pending.
25&100 mg files under Suitability petition. Petition # 99P-4775/CP1

3. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	Date Initials	Date Initials

N/A. Both Barr and Eon hold approvals for the 50mg strength.

4. Pat Beers Block Supv., Review Support Branch EER Status: Refer to the DLPS review below.	Date Initials	Date Initials

Bioequivalence sites:

Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status:
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status:
Reason:

Rwelt 3/19/2002

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:

Patent Certification:
Controlled Correspondence/Cit.Pet:
Comments: RLD =

REVIEWER:

	DRAFT RECEIPT	FINAL ACTION
5. Gregory Davis Supv., Reg. Support Branch	Date 3/19/02 Initials RW	Date 3/19/02 Initials RW

Contains GDEA certification: Yes X No ☐ Determ. of Involvement? Yes ☐ No X
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes X No ☐ Pediatric Exclusivity System
If Para. IV Certification- did applicant P II Date Checked N/A
Notify patent holder/NDA holder Yes ☐ No ☐ Nothing Submitted X
Was applicant sued w/in 45 days: Yes ☐ N/A No ☐ Written request issued ☐
Has case been settled: Yes ☐ No ☐ Study Submitted ☐
Date settled:
Is applicant eligible for 180 day N/A RLD= Revia Tablets 50mg NDA Generic Drugs Exclusivity for each strength: Yes ☐ No X Barr M/as Squibb Pharmaceuticals 18-932
Comments: There are no unexpired patents or exclusivity on the RLD, Revia, tablets. The 25mg and 100mg strengths are unblocked based upon an approved suitability petition, 998-4775/CP1 (change in strength)

6. Peter Rickman Acting Director, DLPS	Date 3/19/02 Initials RW	Date 3/22/02 Sat/for Initials RW

Comments: Bioequivalence studies (fasting for 100mg strength, fasting for 50mg strength) found acceptable 1/11/02. Dissolution data found acceptable. Waiver granted for 25mg strength. Studies conducted by ____. Each of these facilities has an acceptable OSI inspectional history. Office level bio endorsed 1/11/02. CMC acceptable 3/6/02. Methods validation is not required - ALT and drug product are comparable

7. Robert L. West Acting Deputy Director, OGD	Date 3/19/02 Initials RW	Date 3/22/2002 Initials Robert West for

Para.IV Patent Cert: Yes ☐ No X; Pending Legal Action: Yes ☐ No X; Petition: Yes ☐ No X
Comments: The GMP inspection started at the Hallbindkradt facility on 2/25/02 - ACCEES dated 3/20/02 - No O.A.I. alerts noted.

This application is recommended for approval.

8. Gary Buehler Acting Director, OGD	Date 3/22/2002 Initials RW	Date 3/22/2002 Initials Robert West for

Comments: 1-Cycle approval. 4 months, 22 days total time to approval. 16

Janet Woodcock, M.D. Director Center for Drug Evaluation And Research	Date ____ Initials ____	Date ____ Initials ____

First Generic Approval X for 25mg and 100mg strengths PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Review Support Branch	Date 3/22/02 Initials SMS	Date 3/22/02 Initials SMS

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:20PM Time notified of approval by phone 2:23PM Time approval letter faxed

FDA Notification:
3/22/02 Date e-mail message sent to "OGD approvals" account
3/22/02 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-264

CORRESPONDENCE

tyco
Healthcare
Mallinckrodt

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

ORIGINAL APPLICATION

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 06 2001
OGD

October 31, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg)

Dear Madame or Sir:

Mallinckrodt Inc. hereby submits this Abbreviated New Drug Application under 21 C.F.R. § 314.92(a)(1). This ANDA Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg) is a prescription drug for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg) will be manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

This original application consists of eighteen (18) volumes. An archival copy is being filed in blue folders and a technical review copy is being filed in red folders. A separate copy of the bioequivalence section is being submitted in an orange folder. This also certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA was sent to the District Office in Buffalo, NY. This "field copy" is contained in maroon folders. For more detailed information on the organization of this application, please refer to "Executive Summary" which is included immediately following the Table of Contents.

In addition, it is Mallinckrodt's intention that an electronic submission will arrive within 30 days of this paper application. In the event that review of the paper submission is initiated before the electronic submission is received and processed, it is Mallinckrodt's understanding the review will be completed using the hard copy only.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
FAX: 314-654-6496

MALLINCKRODT

12/13/01 NMF S. Middleton

MEB RW

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis, MO 63134 Phone: 314-654-2000 www.mallinckrodt.com

NEW CORRESP
NC

CMC ELECTRONIC SUBMISSION

November 15, 2001

76-264

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg)

Dear Madame or Sir:

On October 31, 2001 pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, Mallinckrodt Inc. submitted the above referenced ANDA. Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg) are a prescription drug for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg) will be manufactured, processed, packaged, labeled, tested for release and stability, held and distributed by Mallinckrodt Inc. at Mallinckrodt's facility in Hobart, New York.

The purpose of this submission is to provide the Agency with a copy of the CMC Electronic Submission ESD and companion document for the above referenced application. The Chemistry, Manufacturing, and Control information is provided in a blue archival folder with the proposed text for the proposed draft package insert in WordPerfect 6.1 format on two 3.5" diskettes. The CMC Electronic Submission ESD and the companion document are provided on a CD.

The information contained on the CDs and the 3.5" diskettes is the same as the paper copy.

In the event that review of the paper submission is initiated before the electronic submission is received and processed, it is Mallinckrodt's understanding the review will be completed using the hard copy only.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
FAX: 314-654-6496

ANDA 76-264

Mallinckrodt Inc.
Attention: Marianne Robb
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134-0840

DEC 12 2001

Dear Madam:

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 also made to the telephone conversation dated December 5, 2001 and your correspondence dated December 10, 2001.

NAME OF DRUG: Naltrexone Hydrochloride Tablets USP, 25 mg, 50 mg and 100 mg

DATE OF APPLICATION: October 31, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 6, 2001

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:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-264
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB _____ date 12 DEC 2001
HFD-615/SMiddleton, CSO _____ date 12/12/01
Word File
V:\FIRMSAM\MALLINCKRODT\LTRS&REV\76264.ack
F/T EEH 12/12/01
ANDA Acknowledgment Letter!

tyco
Healthcare
Mallinckrodt

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

TELEPHONE AMENDMENT TO A PENDING APPLICATION

December 21, 2001

[redacted] CORRESP
NCTD BIO

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 76-264: Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg)

Dear Madame or Sir:

Per 21 C.F.R. § 314.60 and in response to a December 20, 2001 telephone request for additional information from Steven Mazzella of the Agency, Tyco/Mallinckrodt hereby submits this telephone amendment to the above referenced application. This amendment provides a diskette that contains the statistical analysis of the data performed using SAS® software, Version 6.12.

The archival copy of this telephone amendment to a pending application consists of one (1) volume. An archival copy is being filed in a blue folder and the review copy is being filed in an orange folder.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. For additional information, please contact me at 314-654-6258 or James F. Baker, Ph.D., Director, Regulatory Affairs at 314-654-5729.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
FAX: 314-654-6496

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 26 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76264 APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Naltrexone Hydrochloride Tablets, USP, 25 mg, 50 mg, and 100 mg

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as per USP.

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,

Barbara Myers Sanz

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

MODE = MEMORY TRANSMISSION START=FEB-06 14:50 END=FEB-06 14:51

FILE NO.=006

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	913146546496	004/004	00:00:56

-FDA CDER OGD LPS -

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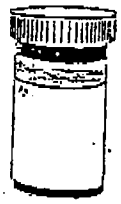
Fax Cover Sheet



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: Feb 6, 02

To: Marianne Robb

Phone: _____ Fax: 314-654-6696

From: Chan Park

Phone: (301) 827-5846 Fax: (301) 443-3647

Number of Pages: _____
(Including Cover Sheet)

Comments: ANDA 76-264 (Naltrexone HCl Tab)
Labeling deficiency Thanks
Chan

N 76264

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

ANDA Number: **76-264** Date of Submission: **October 31, 2001**

Applicant's Name: **Mallinckrodt, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets USP, 25 mg, 50 mg, & 100 mg**

Labeling Deficiencies:

1. CONTAINER - 30s, 100s, & 1000s

   a. Revise the storage temperature statement to read "Store at _____"

   b. Your proposed package size of 30s appears to be a unit-of -use packaging, which requires a child-resistant closure to comply with the Poison Prevention Packaging Act. Please assure that you employ a child-resistant closure for this package size and/or comment.

2. INSERT

   a. GENERAL

      It is preferable to use the term "to" rather than a hyphen to express a range of numerical numbers.

   b. DESCRIPTION

      i. First paragraph, last sentence

         ...4, 5α-epoxy-3, 14... [note "α"]

      ii. Add a bullet to the molecular formula to read "$C_{20}H_{23}NO_4 \bullet HCL$

      iii. Revise the molecular weight to read "377.86" per USP 24.

      iv. Last paragraph - Revise to read:

         In addition, each tablet contains the following inactive ingredients: crospovidone...

   c. CLINICAL PHARMACOLOGY

      You may delete the term "hydrochloride" to read "naltrexone" throughout this section except where "naltrexone hydrochloride" is specifically associated with a dose of this product.

d. INDICATIONS AND USAGE

i. First paragraph:

Naltrexone hydrochloride tablets are...

ii. Naltrexone hydrochloride tablets have not...

e. CONTRAINDICATIONS - Item #2:

2) ...on opioids , including those currently maintained on opiate agonists [e.g., methadone or LAAM (levo-alpha-acetyl-methadol)].

f. WARNINGS

i. See comment under CLINICAL PHARMACOLOGY.

ii. Attempt to Overcome Blockade - First paragraph, last sentence:

...blockade (see **PRECAUTIONS, Information for Patients**).

g. PRECAUTIONS

i. See comment under CLINICAL PHARMACOLOGY.

ii. Information for Patients - Third paragraph, last sentence:

...other opioid (including methadone or LAAM) while on...

h. ADVERSE REACTIONS

See comment under CLINICAL PHARMACOLOGY.

i. DRUG ABUSE AND DEPENDENCE

Naltrexone is a pure...

j. HOW SUPPLIED

i. See comments under CONTAINER.

ii. Your description of 100 mg tablet is not consistent with the one found in your controls for Finished Dosage Form. Specifically, please clarify whether the side with "DEPADE" is partially scored or not

Please revise your container labels and insert labeling, as instructed above, and submit container labels and insert labeling in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

APPEARS THIS WAY
ON ORIGINAL

tyco
Healthcare

mallinckrodt

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION ORIG AMENDMENT

February 11, 2002

N/AA

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 76-264: Naltrexone Hydrochloride Tablets, USP (25 mg, 50 mg, and 100 mg)

Dear Madame or Sir:

The following information is being supplied in response to a February 6, 2002 telephone request from Jeen Min of the Office of Generic Drugs. This certifies that, per 21 C.F.R. §314.440(a)(4) and concurrently with the filing of this telephone amendment to the above referenced ANDA, true copies of the technical sections of the ANDA amendment are being sent to the local district offices.

This amendment to a pending application consists of one volume. An archival copy is being filed in a blue folder and a technical copy is being filed in a red folder. In addition, a field copy is being sent to the district office in Buffalo, New York. This field copy is contained in a maroon folder. For more detailed information on the organization of this application, please refer to the "Executive Summary".

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 13 2002

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submissions
FAX: 314-654-6496

2/5/02

tyco Healthcare
Mallinckrodt

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Tele: 314 654-2000
www.mallinckrodt.com

AMENDMENT TO A PENDING APPLICATION
FINAL PRINTED LABELING

February 18, ~~2001~~ 2002

ORIG AMENDMENT
N/AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 76-264: Naltrexone Hydrochloride Tablets USP
25 mg, 50 mg and 100 mg

Dear Madame or Sir:

The following information is provided in response to a February 6, 2002 facsimile deficiency. This amendment to a pending application consists of one volume, an archival in a blue folder and a technical copy that includes twelve copies of Final Printed Labeling in a red folder.

For more detailed information on the organization of this application, please refer to the "Executive Summary" which is included following the Table of Contents.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or James F. Baker, Ph.D. at (314) 654-5729.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
Phone: (314) 654-6258
Fax: (314) 654-6496