CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

Approval Letter

ANDA 75-274

MAY 26 1999

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated December 15, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naltrexone Hydrochloride Tablets USP, 50 mg.

Reference is also made to your amendments dated April 21, August 24, and November 24, 1998; and February 4, March 15 (2 submissions), April 12 and April 14, 1999.

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 Dupont Merck Pharmaceutical Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising,

and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

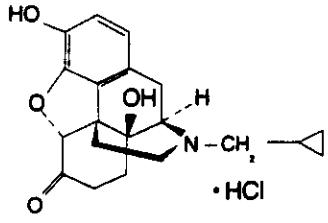
FINAL PRINTED LABELING

7947-01

Naltrexone Hydrochloride Tablets

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 has the chemical name of 17-(Cyclopropylmethyl)-4, 5 α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride. The structural formula is as follows:



naltrexone hydrochloride

$C_{20}H_{23}NO_4 \cdot HCl$ M.W. 377.87

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, for oral administration, are available in scored tablets containing 50 mg of naltrexone hydrochloride.
Naltrexone hydrochloride tablets also contain: carnauba wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, anhydrous lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, colloidal silicon dioxide, silicon dioxide, titanium dioxide and yellow iron oxide.

CLINICAL PHARMACOLOGY:
Pharmacodynamic Actions: Naltrexone hydrochloride 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 Cmax 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 98% 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 tablets 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic measures 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 mg once daily or placebo. In this study, naltrexone hydrochloride proved superior to placebo in measures of drinking including abstinence 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 effect 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-acetylmethadol) 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 7-10 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 has 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.
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 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. daily) 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 pharmacological 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 concentrations 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 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 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 with Naltrexone: 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 patients experience of the full range of the 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 the patients with renal impairment.

Hepatic Impairment: Cautions 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**).

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.
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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 932; or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and transaminase levels of all patients on whom follow-up was obtained returned to (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.

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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 it 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 with Naltrexone: 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 patients experience of the full range of the 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 the patients with renal impairment.

Hepatic Impairment: Cautions 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 tablets 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 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 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.

Carcinogenesis:

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/m²/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/m²/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.

Mutagenesis:

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.

Impairment of Fertility:

Naltrexone (100 mg/kg/day [600 mg/m²/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, Teratogenic Effects: Pregnancy: Category C. The following statements based on the results of experiments in rats. The potential reproductive toxicity of the metabolite 6-β-naltrexol in rats is not known.

Naltrexone has been shown to have an embryocidal and fetotoxic effects in rats and rabbits when given in dosages 30 and 60 times, respectively, the human dose. There are no adequate and well-controlled studies in pregnant women. Naltrexone should be used in pregnancy only when the potential benefit justifies the potential risk to the fetus.

Naltrexone increased the incidence of early fetal loss when administered to rats in oral doses ≥ 30 mg/kg/day (180 mg/m²/day; 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (720 mg/m²/day; 16 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).

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

Nursing Mothers: 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, AND 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 **CLINICAL PHARMACOLOGY, 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 EVENT	
	Naltrexone	Placebo
Depression	0-15%	0-17%
Suicide Attempt/Ideation	0-1%	0-3%

Although no casual 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, and 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, elevation in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitation, myalgia, anxiety, confusion, euphoria, hallucination, 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 casual 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 base line levels of some hypothalamic, pituitary, or gonadal hormones. The clinical significance of such changes is not fully understood.

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.

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

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 ± 96 mg /kg; 1,450 ± 285 mg/kg; and 1,490 ± 102 mg /kg, respectively. In acute toxicity studies in the mouse, rat, and dog, cause of death was 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 overdosage, 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 **CLINICAL PHARMACOLOGY, Individualization of Dosage**). 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 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 7-10 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. 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 hydrochloride.
Observe for 30 seconds for signs or symptoms of withdrawal.
If no evidence of withdrawal, inject 0.6 mg of naloxone hydrochloride.
Observe for an additional twenty minutes.

Subcutaneous:
Administer 0.8 mg of naloxone hydrochloride.
Observe for 20 minutes for signs or symptoms of withdrawal.
Note: Individual patients, especially those with opioids dependency, may respond to lower doses of naloxone. In some cases 0.1 mg IV naloxone hydrochloride 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, runny nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep pattern, 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, sensation of skin crawling, or fasciculation. 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 are any doubts about the results 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., the 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 **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Patient Compliance: Naltrexone should be considered as only one of the 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 50 mg, are available as yellow, film-coated, capsule-shaped tablets, debossed "A 105" on bisected side and supplied in bottles of 30's and 500's.

Store at 25°C, with brief excursions permitted between 15°C and 30°C (59°-86°F), controlled room temperature, see USP.

MANUFACTURED BY
AMIDE PHARMACEUTICAL, INC.
101 East Main Street Little Falls, NJ 07424 USA

4/99

Amide
PHARMACEUTICAL, INC.

NDC 52152-105-30

NALTREXONE
HYDROCHLORIDE
TABLETS
50 mg

Rx only

30 TABLETS

Each Tablet Contains:
Naltrexone Hydrochloride ..... 50 mg

Usual Adult Dosage: For dosage and full prescribing information, read accompanying product information.

Store at 25°C with brief excursions permitted between 15°C and 30°C (59° to 86°F), controlled room temperature, see USP.

Dispense in a tight container as defined in the USP.

N 3 52152-105-30 1

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:

Exp. Date:

7945-01 26 1999

NDC 52152-105-30

NALTREXONE
HYDROCHLORIDE
TABLETS
50 mg

Rx only

30 TABLETS

Usual Adult Dosage: For dosage and full prescribing information, read accompanying product information.

Store at 25°C with brief excursions permitted between 15°C and 30°C (59° to 86°F), controlled room temperature, see USP.

Dispense in a tight container as defined in the USP.

26 1999

N 3 52152-105-30 1

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:

Exp. Date:

7945-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-105-04

NALTREXONE
HYDROCHLORIDE
TABLETS
50 mg

Rx only

500 TABLETS

Each Tablet Contains:
Naltrexone Hydrochloride ..... 50 mg

Usual Adult Dosage: For dosage and full prescribing information, read accompanying product information.

Store at 25°C, with brief excursions permitted between 15°C and 30°C (59°-86°F), controlled room temperature, see USP.

Dispense in a tight container as defined in the USP.

N 3 52152-105-04 2

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:

Exp. Date:

7946-01 26 1999

Amide
PHARMACEUTICAL, INC.

NDC 52152-105-04

NALTREXONE
HYDROCHLORIDE
TABLETS
50 mg

Rx only

500 TABLETS

Each Tablet Contains:
Naltrexone Hydrochloride ..... 50 mg

Usual Adult Dosage: For dosage and full prescribing information, read accompanying product information.

Store at 25°C, with brief excursions permitted between 15°C and 30°C (59°-86°F), controlled room temperature, see USP.

Dispense in a tight container as defined in the USP.

N 3 52152-105-04 2

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:

Exp. Date: 26 1999

7946-01

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

CHEMISTRY REVIEW(S)

ANDA 75-274

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-274

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Revia (Naltrexone Hydrochloride Tablets), 50 mg of DuPont Pharma.

The applicant certifies that to the best of their knowledge, the patent for Naltrexone Tablets expired in 1994.

The applicant certifies that they are not requesting exclusivity for Naltrexone Tablets and that exclusivity will not be claimed for use in alcohol dependence until the exclusivity expires in December 1997.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Naltrexone Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: December 15, 1997
New Corresp (Drug subs): January 12, 1998
Amendment (Analytical methods): April 21, 1998
Amendment (Bio): April 21, 1998
Amendment (Chem): Aug 24, 1998
Amendment (Label): Nov. 24, 1998
Amendment (Chem): Feb 4, 1999
Amendment (Chem): March 15, 1999

FDA:
Acknowledgement: January 12, 1998
Memo (CGMP inspection): February 25, 1998
Deficiency letter (Bio): March 31, 1998
Deficiency letter (Chem): June 30, 1998
Deficiency letter (chem): Mar 12, 1999

10. PHARMACOLOGICAL CATEGORY
Opioid antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

ANDA 75-274

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

Naltrexone Hydrochloride
$C_{20}H_{23}NO_4.HCl$; M.W. = 377.87

17-(Cyclopropylmethyl)-4,5□-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. CAS [16676-29-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable. Need final label AC worksheet.

19. REVIEWER:
A. Langowski

DATE COMPLETED:
03/31/99

Page(s) 13

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Ministry Review # 3

3/31/99

ANDA 75-274

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-274

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Revia□ (Naltrexone Hydrochloride Tablets), 50 mg of DuPont Pharma.

The applicant certifies that to the best of their knowledge, the patent for Naltrexone Tablets expired in 1994.

The applicant certifies that they are not requesting exclusivity for Naltrexone Tablets and that exclusivity will not be claimed for use in alcohol dependence until the exclusivity expires in December 1997.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Naltrexone Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
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New Corresp (Drug subs): January 12, 1998
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Amendment (Chem): March 15, 1999

FDA:
Acknowledgement: January 12, 1998
Memo (CGMP inspection): February 25, 1998
Deficiency letter (Bio): March 31, 1998
Deficiency letter (Chem): June 30, 1998
Deficiency letter (chem): Mar 12, 1999

10. PHARMACOLOGICAL CATEGORY
Opioid antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

ANDA 75-274

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

Naltrexone Hydrochloride
$C_{20}H_{23}NO_4.HCl$; M.W. = 377.87

17-(Cyclopropylmethyl)-4,5□-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. CAS [16676-29-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable. Need final label AC worksheet.

19. REVIEWER:
A. Langowski

DATE COMPLETED:
03/31/99

Page(s) 2

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Information and are not

releasable.

No Date

Chemistry Comments

#38

STATUS REPORT FOR CHEMISTRY DOCUMENTS INTENDED TO BE FAXED

Please check appropriate boxes to indicate the status of other application features when preparing a fax/minor/major def. Fax:

Feature	Pending	Acceptable /Comments Attached	Not Accept/ Comments Attached	Other (i.e. not needed, already sent)
BIO		✓ sent already		
LABELING	✓ Pending Review			
METHODS VAL. SPL.	NA	✓		
EIR		✓ 17-APR-98		
MICRO				

ANDA #: 75-274 DATE: 2/23/99

Project Manager:

Bonnie McNeal _____
Denise Huie _____
Joe Buccine _____
Mark Anderson _____
Kassandra Sherrod _____
Tim Ames ✓

ANDA 75-274

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-274

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Revia (Naltrexone Hydrochloride Tablets), 50 mg of DuPont Pharma.

The applicant certifies that to the best of their knowledge, the patent for Naltrexone Tablets expired in 1994.

The applicant certifies that they are not requesting exclusivity for Naltrexone Tablets and that exclusivity will not be claimed for use in alcohol dependence until the exclusivity expires in December 1997.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Naltrexone Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: December 15, 1997
New Corresp (Drug subs): January 12, 1998
Amendment (Analytical methods): April 21, 1998
Amendment (Bio): April 21, 1998
Amendment (Chem): Aug 24, 1998
Amendment (Label): Nov. 24, 1998

FDA:
Acknowledgement: January 12, 1998
Memo (CGMP inspection): February 25, 1998
Deficiency letter (Bio): March 31, 1998
Deficiency letter (Chem): June 30, 1998

10. PHARMACOLOGICAL CATEGORY
Opioid antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

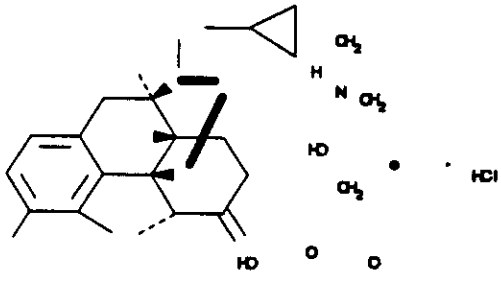
ANDA 75-274

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

Naltrexone Hydrochloride
$C_{20}H_{23}NO_4.HCl$; M.W. = 377.87



17-(Cyclopropylmethyl)-4,5 -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. CAS [16676-29-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
See item #38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable.

19. REVIEWER:
A. Langowski

DATE COMPLETED:
02/08/99

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Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2
2/8/99

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (201) 890-1440
Fax (201) 890-7980

January 12, 1998

Denise Huie
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NAI, EES filed already 1/20/98

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Ms. Huie:

Per our telephone conversation of January 9, 1998, the manufacturing site address for the bulk active, Naltrexone Hydrochloride manufactured by is as follows:

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
JAN 13 1998
GENERIC DRUGS

Page(s) _____

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releasable.

6/30/98

Chemistry Community

#5

ANDA 75-274

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-274

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Revia™ (Naltrexone Hydrochloride Tablets), 50 mg of DuPont Pharma.

The applicant certifies that to the best of their knowledge, the patent for Naltrexone Tablets expired in 1994.

The applicant certifies that they are not requesting exclusivity for Naltrexone Tablets and that exclusivity will not be claimed for use in alcohol dependence until the exclusivity expires in December 1997.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Naltrexone Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submited: December 15, 1997
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FDA:
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10. PHARMACOLOGICAL CATEGORY
Opioid antagonist

11. Rx or OTC
Rx

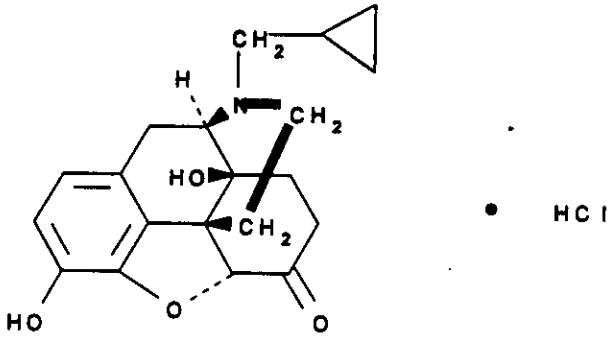
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE

Naltrexone Hydrochloride
$C_{20}H_{23}NO_4.HCl$; M.W. = 377.87



17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. CAS [16676-29-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. Chemistry, manufacturing and control deficiencies remain.
b. Label review is pending as of 5/15/98.
c. Bio review is pending for the 4/21/98 amendment.
d. Request for methods validation is deferred

18. CONCLUSIONS AND RECOMMENDATIONS

The application is NOT APPROVABLE. The amendment will be MAJOR.

19. REVIEWER:
Donald Shostak

DATE COMPLETED:
May 18, 1998

Page(s) 17

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Information and are not

releasable.

5/13/98

Chemistry Review # 1

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

BIOEQUIVALENCE REVIEW(S)

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

April 21, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AB

BIOEQUIVALENCE AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the bioequivalency deficiency dated March 31, 1998, following is the amendment to our ANDA 75-274, Naltrexone Tablets 50 mg.

1. The *in vitro* dissolution testing on your naltrexone HCl 50 mg tablets is not acceptable.

   The dissolution should be conducted at least up to 60 minutes in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

   minutes.

Response: Amide has performed the comparative dissolution profile of Amide's Naltrexone Tablets and DuPont Pharma's Revia tablets. Enclosed find the results for the dissolution data.

If you or your staff have any question, please feel free to contact us.

RECEIVED
APR 22 1998
GENERIC DRUGS

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

1.1

27 1999

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-274 APPLICANT: Amide

DRUG PRODUCT: Naltrexone HCl 50 mg tablets

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

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

Sincerely yours,

/S/

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

MAR 31 1998

BIOEQUIVALENCY DEFICIENCY

ANDA/AADA: 75-274 APPLICANT: Amide Pharmaceuticals

DRUG PRODUCT: Naltrexone 50 mg tablet.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. The *in vitro* dissolution testing on your naltrexone HCl 50 mg tablets is not acceptable.

   The dissolution should be conducted at least up to 60 minutes in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

Sincerely yours,

/S/

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

Naltrexone HCl

Tablets, 50 mg
ANDA # 75-274
Reviewer: Gur J.P. Singh
File #75274SD.D97

Amide Pharmaceuticals

101 East Main Street
Little Falls , NJ 80223
Submission Date:
December 15, 1997

Review of a fasting bioequivalence study & dissolution data

The sponsor has submitted a fasting study and dissolution data on its naltrexone HCl 50 mg tablets.

Reference Listed Drug

Drug Product:	REVIA® 50 mg tablets manufactured by Dupont Merck.
Indication:	Treatment of a variety of alcohol dependence and for blockade of the effects of exogenously administered opioids.
Bioavailability:	Completely absorbed following oral administration.
Metabolites:	Approximately 40-95% of the absorbed naltrexone undergoes first-pass metabolism. 6-beta-naltrexol is the principal metabolite with opioid receptor blocking activity. Two other minor metabolites include 2-hydroxy-3-methoxy-6-beta-naltrexol and 2-hydroxy-3-methoxy-naltrexone.
Half Life:	Approximately 1.1-10 hours for naltrexone, and 12-14 hours for 6-beta-naltrexol.
T_{max}:	Approximately 1 hour for naltrexone and 6-beta-naltrexol.
Excretion:	Approximately 60% of the dose may be excreted in urine.
Food Effect:	Not known. Hitherto, DBE* has not required food study on naltrexone HCl tablets.
DBE guidance:	Not available. For determination of bioequivalence, DBE relies on bioavailability data for two species, naltrexone and 6-beta-naltrexol.

* *Division of Bioequivalence*

Fasting Bioequivalence Study

OBJECTIVE: The purpose of this study was to establish bioequivalence of Amide Pharmaceuticals' naltrexone HCl 50 mg tablets to Dupont Merck's REVIA® 50 mg tablets.

STUDY SITE, INVESTIGATORS AND DATES:

Clinical Study site:
Analytical Study Site:

Medical Director:
Analytical Director:

Study Protocol:	Protocol (#AAI-US-18, August 22, 1997, pp 198-211, vol 1.1) was approved by the
Dosing Dates:	September 13-27, 1997
Analytical Dates:	October 13-27, 1997.

SUBJECT SELECTION:

Twenty seven (27) healthy male volunteers were enrolled for this study. The age and weight of these volunteers were in the range of 19 - 44 years and 114 - 228 lbs, respectively (pp 218, vol 1.1). Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria (pp 201, vol 1.1)

STUDY DESIGN: The clinical study was conducted as a single dose, randomized, two-treatment, two-period crossover evaluation. The first dosing date for subjects 23, 24, 25, 26 and 28 was different from the remaining twenty two subjects, whereas the dosing date for the second period was same for all subjects. Therefore the washout period for the five subjects was 7 days, and it was 14 days for the remaining 22 subjects.

TREATMENTS:

A: Naltrexone HCl tablets 1x50 mg, Amide Pharmaceuticals, (Lot #: 729A2A, Lot Size:

B: REVIA^{R} tablets 1x50 mg, Dupont Merck (Lot #: LD157A, Lot Size: Commercial lot, Expiry Date - 4/99).

The randomization sequence used in the study is given in the table 2 (attachment).

DOSING AND MEALS:

After an overnight (10 hours) fast, each drug was given orally with 240 mL of water. Within one hour before and one hour after dosing only water supplied was with drug administration. Subjects were served standard lunch 4 hours after dosing, and meals/snacks thereafter.

SAMPLE COLLECTION AND STORAGE:

Sample:	Venous blood collected in heparin containing Vacutainer® tubes.
Sampling times:	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48 and 60 hours after dosing.
Sample Storage:	Plasma was separated and stored at -20°C until analysis.

HEMODYNAMIC EVALUATIONS: The protocol did not include hemodynamic measurements.

ANALYTICAL PROCEDURE (Not to be released under FOI):

Calibration Standards' (CS) and Quality Control (QC) samples' concentrations:

Naltrexone:	CS	0.1. 0.25, 1, 2, 10, 20 and 50 (ng/mL)
	QC	0.25, 5 and 45 (ng/mL)
6-beta-naltrexol:	CS	0.5, 1, 5, 10, 50, 100 and 250 (ng/mL)
	QC	1.25, 25 and 225 (ng/mL)

Specificity: No interfering peaks were detected in representative chromatograms for the blank plasma samples and the zero-hour study samples (vol 1.2).

Limit of Quantitation:

Naltrexone:	0.1 ng/mL (Precision: 1.6 %. Accuracy: 100%).
6-beta-naltrexol:	0.5 ng/mL (Precision: 1.3%. Accuracy: 99%).

Linearity: Calibration curves were linear in the range of calibration standards used ($r^2 \geq 0.99$, pp 719-720, vol 1.2).

Recovery: Mean recoveries (pp 695-28 to 695-30, vol 1.2):

Naltrexone:	90.4%, 89.7% and 90.0%, for samples spiked at concentrations of 0.3, 3 and 30 ng/mL, respectively.
6-beta-naltrexol:	90.0%, 89.1% and 89.4% for samples spiked at concentrations of 1.5, 15 and 150 ng/mL, respectively.
Internal Standard:	88.5%

Stability: The firm has demonstrated naltrexone and 6-beta-naltrexol stability in frozen samples for approximately 62 days and its in-process and freeze thaw stability (vol 1.2) .

Reproducibility and Accuracy :

Intra-day (pre-study validation):

	Precision	Accuracy
Naltrexone:	0.4%-1.2%	89%-101%
6-beta-naltrexol:	0.3%-0.6%	99%-100%

Inter-day (Within the sample analysis period, based on CS and QC samples):

	Precision	Accuracy	
Based on CS:			
Naltrexone:	0.6%-1.4%	99%-100%	(pp 736, vol 1.2)
6-beta-naltrexol:	0.5%-2.4%	99%-100%	(pp 753, vol 1.2)
Based on QC samples:			
Naltrexone:	1.2%-1.6%	100%-102%	(pp 751, vol 1.2)
6-beta-naltrexol:	8.3%-11.1%	100%-101%	(pp 768, vol 1.2)

Repeat Assays: In this study five plasma samples were reanalyzed (see pp 717, vol 1.2). These samples represent <1% of all study samples analyzed.

Analytical Method Deficiencies: None

PHARMACOKINETIC (PK) DATA ANALYSIS:

PK Parameters: AUC_{0-t} (AUC), $AUC_{0-infinity}$ (AUCI), C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el} were computed. Parameter values were calculated for naltrexone and 6-beta-naltrexol. The reviewer has verified the AUC and AUCI values. Differences between AUC values obtained by the reviewer and those submitted by the firm were <1%. Therefore parametric data submitted by the firm were considered to be accurate and used by the reviewer for all statistical analyses.

Statistical analyses: Analysis of variance (ANOVA) with subjects, period and treatment as factors, and sequence as between subject factor was applied to PK parameters and plasma concentrations at each sampling time point. Statistical analyses of pharmacokinetic data were conducted using the t-test method to determine differences between naltrexone HCl formulations in AUC, AUCI and C_{max} at $\alpha = 0.05$ and $\beta = 0.20$.

As mentioned in the Study Design section, the first dosing date for five subjects was different from the remaining 22 subjects. However, the sponsor used the standard ANOVA model which is not appropriate for a study with three dosing periods, as employed in this study. Therefore the reviewer has performed ANOVA based on two models, (1) the standard model used for the two-period two-way crossover studies, and (2) a modified model for a three-period two-way crossover study. Bioequivalence evaluations based on both analyses are presented in this review.

RESULTS:

Clinical Study Conduct:

Number of subject dosed	27
Number of subjects completing the study:	25 (Subject #15 dropped due personal reasons, subject #20 was dropped due to poor venous access).
Adverse events:	Three adverse events were reported (pp 224, vol 1.1). One of these events (emesis, subject #12) was considered to be possible drug related. The emesis occurred soon after the observed T_{max}. Exclusion of that subject from statistical analysis did not affect the outcome this study.
Protocol deviations:	Deviations in the scheduled times for blood draws were reported (pp 222, vol 1.1). In reviewer's opinion, these deviations should not influence bioequivalence evaluation.

PK Data:

Individual-subject plasma concentration data : Naltrexone (pp 302-304, vol 1.1) and 6-beta-naltrexol (502-504, vol 1.1). Line graphs depicting individual-subject concentration vs time profiles are presented in the following portions of the ANDA: Naltrexone (pp 240-264 & 468-490, vol 1.1) and 6-beta-naltrexol (pp 671-695, vol 1.1).

First nonzero time concentration reported as C_{max}: None

Mean plasma concentration profiles: See table 1 (attachment).

AUC, AUCI and C_{max} data: See table 2 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioequivalence Evaluation:

Mean parametric values and test/ref ratios: see table 3 (attachment).

90% confidence intervals: As mentioned above, the ANOVA was performed using a two-period and a three-period model. The 90% confidence intervals were within the acceptable limit of 80-125% for naltrexone and 6-beta-naltrexol, based on both analyses.

Sequence Effect: Not detected based on reviewer's and sponsor's analyses.

Bioequivalence Study Deficiencies: None

In Vitro Dissolution Testing

Method: There is no USP monograph for naltrexone HCl tablets. The sponsor did not use testing conditions currently recommended by DBE.
Test and reference products: Lots of the 50 mg tablets of the test and reference products used for dissolution testing and the bioequivalence study were identical.
Results: Dissolution testing is summarized in table 4 (attachment). Dissolution testing does not meet Agency specifications (see the Comments section).

Test Product Composition (Not to be released under FOI):

Ingredient	mg/Tablet
see package insert	

Waiver Request: Not applicable.

Comments

1. This firm conducted a fasting bioequivalence study on its naltrexone HCl 50 mg tablet and the reference product, REVIA®50 mg tablet in 27 healthy male subjects.

2. Bioequivalence evaluation is based on 25 subjects' data for naltrexone and 6-beta-naltrexol. Based on reviewer's calculations, the AUC, AUCI and C_{max} 90% confidence intervals for both chemical moieties were within the acceptable limit of 80-125%.

3. The results of this study demonstrate that under fasting conditions, Amide Pharmaceuticals' naltrexone HCl 50 mg tablet is bioequivalent to the reference product, REVIA® 50 mg tablet.

4. The *in vitro* dissolution data submitted by the firm on its 50 mg naltrexone HCl tablet are not acceptable because:

   A. The sponsor tested dissolution in 0.1N HCl, instead of water recommended hitherto by DBE for dissolution testing on multisource naltrexone HCl tablets.

B. The sponsor tested dissolution for 45 minutes. The agency specification for dissolution testing on naltrexone HCl tablets is "Not less than 80% in 60 minutes". Dissolution testing should be performed at least up to 60 minutes.

Recommendations

1. The *in-vivo* bioequivalence study conducted under fasting condition by Amide Pharmaceuticals on its naltrexone HCl 50 mg tablet, lot #729A2A, comparing it to the reference product REVIA® 50 mg tablet, lot #LD157A, manufactured by Dupont Merck, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Amide Pharmaceuticals' naltrexone HCl 50 mg tablets are bioequivalent to REVIA® 50 mg tablets, manufactured by Dupont Merck.

2. The *in vitro* dissolution testing conducted by Amide Pharmaceuticals on its naltrexone HCl 50 mg tablets is not acceptable.

   The dissolution should be conducted at least up to 60 minutes in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

ge

5. From the bioequivalence point of view, the firm has not met the requirements *in vitro* dissolution testing. The application is therefore incomplete.

/S/

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

3/23/98

/S/

CONCUR: _____ DATE: 3/27/98

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence.

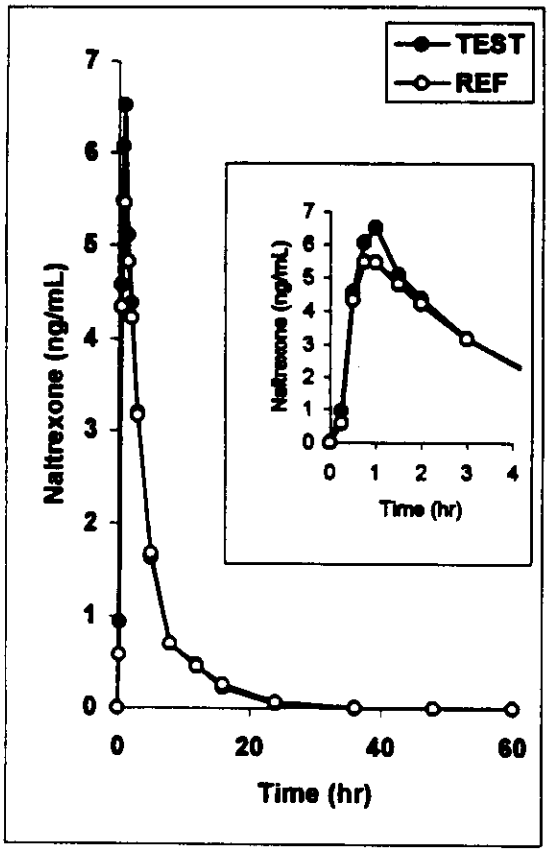
/S/

GJP SINGH 3/18/98 75274SD.D97

Table 1: Mean plasma concentrations (ANDA #75-274)

(Data are based on reviewer's calculations)

Time	Naltrexone (ng/mL) N = 25					6-beta-naltrexol (ng/mL) N= 25				
	TEST		REF		TEST/REF	TEST		REF		TEST/REF
(Hr)	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
0	0.00	0.00	0.00	0.00	-	0.00	0.00	0.00	0.00	-
0.25	0.94	1.51	0.58	1.01	1.63	14.33	23.35	8.47	10.54	1.69
0.5	4.57	4.94	4.34	4.21	1.05	53.84	36.01	61.13	42.94	0.88
0.75	6.06	4.73	5.48	3.23	1.11	70.59	29.54	71.80	33.84	0.98
1	6.51	5.06	5.46	2.76	1.19	70.83	25.98	67.09	28.13	1.06
1.5	5.11	2.98	4.82	2.21	1.06	57.72	14.69	57.87	16.33	1.00
2	4.38	2.30	4.23	1.95	1.04	54.96	14.60	53.13	13.01	1.03
3	3.19	1.63	3.16	1.42	1.01	45.92	12.83	46.06	11.19	1.00
5	1.63	1.01	1.68	0.68	0.97	35.74	10.66	35.79	8.58	1.00
8	0.69	1.46	0.70	0.26	0.99	24.99	6.74	25.07	6.24	1.00
12	0.47	2.27	0.45	0.21	1.04	18.61	4.59	18.08	4.47	1.03
16	0.22	3.10	0.25	0.17	0.86	13.94	3.99	14.25	3.87	0.98
24	0.05	4.70	0.06	0.11	0.75	9.46	2.98	9.98	3.54	0.95
36	0.00	-	0.01	0.04	-	4.93	2.25	5.10	2.23	0.97
48	0.00		0.00	0.00	-	2.88	1.43	2.94	1.29	0.98
60	0.00		0.00	0.00	-	1.50	0.94	1.60	0.82	0.94



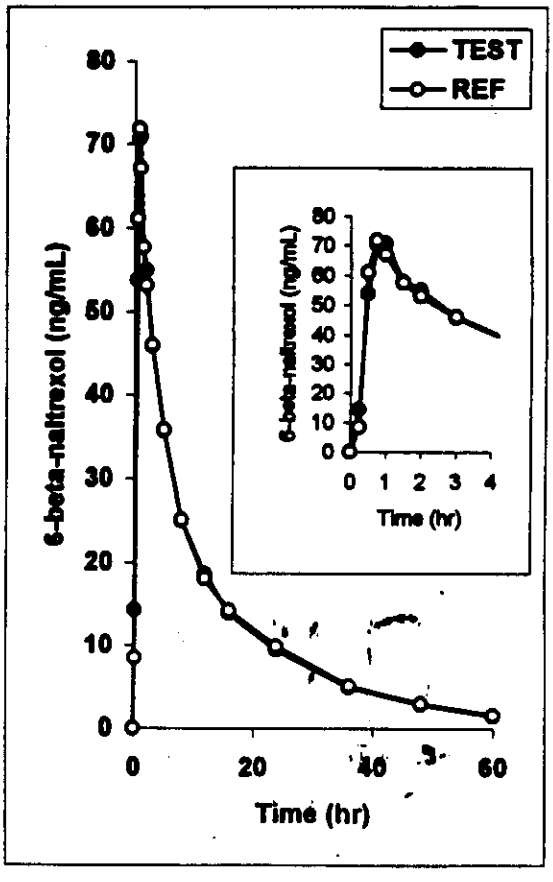


Table 2: Individual subject bioavailability parameter values and Test/Ref ratios (ANDA# 75-274)

Naltrexone

			TEST				REF				TEST/ REF		
SUB	PER	SEQ	AUC (A)	AUCI (B)	A/B	Cmax	AUC (C)	AUCI (D)	C/D	Cmax	AUC	AUCI	Cmax
1	1	AB											
2	2	BA											
3	1	AB											
4	2	BA											
5	1	AB											
6	1	AB											
7	1	AB											
8	2	BA											
9	1	AB											
10	1	AB											
11	2	BA				0							
12	2	BA				00							
13	2	BA											
14	2	BA											
16	1	AB											
17	1	AB											
18	2	BA											
19	2	BA											
21	1	AB											
22	2	BA											
23	2	B											
24	1	A											
25	2	F											
26	1												
28	2	F											
		Mean	24.46	26.05	0.93	7.25	25.53	26.93	0.93	7.57	0.98	1.02	1.14
		S.D.	11.06	10.83	0.04	4.64	11.48	11.46	0.05	5.43	0.23	0.24	0.53

6-beta-naltrexol

SUB	PER	SEQ	TEST AUC (E)	TEST AUCI (F)	TEST E/F	TEST Cmax	REF AUC (G)	REF AUCI (H)	REF G/H	REF Cmax	TEST/REF AUC	TEST/REF AUCI	TEST/REF Cmax
1	1	AB											
2	2	BA											
3	1	AB											
4	2	BA											
5	1	AB											
6	1	AB											
7	1	AB											
8	2	BA											
9	1	AB											
10	1	AB											
11	2	BA											
12	2	BA											
13	2	BA											
14	2	BA											
16	1	AB											
17	1	AB											
18	2	BA											
19	2	BA											
21	1	AB											
22	2	BA											
23	2	BA											
24	1	AB											
25	2	BA											
26	1	AB											
28	2	BA											
		Mean	711.16	752.75	0.96	84.13	759.33	787.25	0.96	88.13	0.94	0.94	1.04
		S.D.	175.90	180.72	0.02	28.38	193.63	217.45	0.02	34.50	0.10	0.11	0.41

TABLE 3: Parametric data , ANDA #75-274

Naltrexone

PARAMETER	TEST		REF		TEST/REF	90% CI*	
	Mean	SD	Mean	SD		2-Period Analysis	3-Period Analysis
AUC (ng/mL*hr)	24.46	11.1	25.53	11.5	0.96	**88.36 - 104.45**	**88.13 - 103.92**
AUCI (ng/mL*hr)	26.05	10.8	26.92	11.5	0.97	**90.65 - 109.88**	**89.80 - 110.13**
Cmax (ng/mL)	7.25	4.6	7.57	5.4	0.96	**85.11 - 121.88**	**87.05 - 121.89**
Tmax (hr.)	0.89	0.5	1.19	0.6	0.75		
kel (1/hr)	0.158	0.063	0.163	0.067	0.97		
t1/2 (hr)	5.16	2.3	5.43	3.6	0.95		

6-beta-naltrexol

PARAMETER	TEST		REF		TEST/REF	90% CI*	
	Mean	SD	Mean	SD		2-Period Analysis	3-Period Analysis
AUC (ng/mL*hr)	711.16	175.9	759.33	193.6	0.94	**90.13 - 97.30**	**90.05 - 97.12**
AUCI (ng/mL*hr)	752.74	180.7	787.25	217.5	0.96	**89.49 - 97.66**	**89.60 - 97.60**
Cmax (ng/mL)	84.13	28.4	88.13	34.5	0.95	**85.40 - 110.43**	**86.18 - 111.31**
Tmax (hr.)	0.88	0.5	1.28	0.7	0.69		
kel (1/hr)	0.053	0.006	0.052	0.009	1.02		
t1/2 (hr)	13.23	1.6	13.65	2.3	0.97		

**** Based on ANOVA performed by the reviewer.***

Table 4: *In vitro* Dissolution Testing

Drug (Generic Name): **Naltrexone HCl Tablet**
Dose Strength: 50 mg
ANDA # **75-274**
Firm. **Amide Pharmaceuticals, Inc.**
Submission Date: December 15, 1997
File Name: **75274SD.D97**

I. Conditions of *in vitro* dissolution testing:

USP XXII Paddle. RPM: 50
No. Units tested: 12
Medium: 900 mL of 0.1N HCl. *The Agency requires 900 mL of water.*
FDA Specification : NLT 80% (Q) in 60 minutes, USP has no specifications for this product
Reference Drug : REVIA 50 mg tablets, manufactured by Dupont Merck.

II. Results of *in vitro* dissolution testing:

Sampling Time (min)	Test Product Lot # 7292A Strength: **50 mg**			Reference Product Lot # LD157A Strength: **50 mg**		
	Mean (%)	Range (%)	CV (%)	Mean (%	Range (%)	CV (%)
15	88.3		2.2	54.8		7.8
30	92.1		1.7	80.3		3.5
45	95.3		1.5	96.8		1.4

Raw dissolution data are given on page 1028 (vol 1.4).

3/27/98
9:20-9:30

ANDA # 75-274
Naltrexone

	PER1	PER2	PER3
22 Subjects	T		T
	R		R
5 Subjects		T	T
		R	R

CODE the Study as having 3 periods.
RUN the standard PROC GLM ~~of PROC MIXED~~
Model for Bioequivalence.

Karen Higgins

BIOEQUIVALENCY DEFICIENCY

ANDA/AADA: 75-274 APPLICANT: Amide Pharmaceuticals

DRUG PRODUCT: Naltrexone 50 mg tablet.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. The *in vitro* dissolution testing on your naltrexone HCl 50 mg tablets is not acceptable.

   The dissolution should be conducted at least up to 60 minutes in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

Sincerely yours,

/S/

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

Layout

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 75-274 **SPONSOR:** Amide
DOSAGE FORM: Naltrexone HCl tablets,
STRENGTHS(s): 50 mg
TYPE OF STUDY: Single dose, Fasting Study
STUDY SITE: AAI Clinic, Chapel Hill, NC

STUDY SUMMARY: Bioequivalence study on naltrexone 50 mg tablets is acceptable.

DISSOLUTION: Dissolution testing on naltrexone 50 mg tablets meets Agency specifications.

WAIVER REQUESTS: NA

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE 7-13-98

TEAM LEADER: Shriniwas G. Nerurkar, Ph D. **BRANCH:** II

INITIAL: /S/ DATE 7/16/1998

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE 7/21/98

DIRECTOR, OFFICE OF GENERIC DRUGS: Douglas Sporn

INITIAL: _____ DATE _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-274 APPLICANT: Amide

DRUG PRODUCT: Naltrexone HCl 50 mg tablets

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

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

Sincerely yours,

/S/

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

Table 1: *In vitro* Dissolution Testing

Drug Product: **Naltrexone Tablets**
Dose Strength: 50 mg

ANDA # 75-274, the raw data are given in vol. 1.1
Firm: **Amide**
Submission Date: April 21, 1998
File # **75274D.498**

Conditions of Dissolution Testing:

USP Apparatus 2 Paddle, RPM:50
Units Tested: 12
Media: 900 mL of water
Specifications (Agency):

Reference Drug: Revia[R] 50 mg tablets

Results of Dissolution Testing:

Sampling Time (min)	Test Product Lot # 7292A Strength: 50 mg			Reference Product Lot # LD157A Strength: 50 mg			T/R
	Mean (%)	Range (%)	CV (%)	Mean (%)	Range (%)	CV (%)	
15	86.1		1.9	60.4		5.7	1.43
30	89.6		1.9	85.1		2.9	1.05
45	89.8		1.8	96.3		1.7	0.93
60	91.7		1.6	100.4		1.3	0.91

Naltrexone HCl
Tablets, 50 mg
ANDA # 75-274
Reviewer: Gur J.P. Singh
File #75274D.498

Amide Pharmaceuticals
101 East Main Street
Little Falls , NJ 80223
Submission Date:
April 21, 1998

Review of a Bioequivalence Amendment

The sponsor submitted a fasting study and dissolution data on its naltrexone HCl 50 mg tablets on December 15, 1997. A review of that submission was completed on March 27, 1998. The fasting bioequivalence study was found to be acceptable. However, dissolution testing was considered to be unsatisfactory, and the following deficiency was communicated to the firm.

> *"The in vitro dissolution testing on your naltrexone HCl 50 mg tablets is not acceptable.*
>
> *The dissolution should be conducted at least up to 60 minutes in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:*
>
> A
> 6- .....

On April 21, 1998, the firm provided addition dissolution data. A review of these data is as follows:

Method: There is no USP monograph for naltrexone HCl tablets. The sponsor used testing conditions currently recommended by DBE.

Test and reference products: Lots of the 50 mg tablets of the test and reference products used for dissolution testing and the bioequivalence study were identical.

Results: Dissolution testing is summarized in table 1 (attachment). Dissolution testing meets Agency specifications.

COMMENTS

1. The *in vitro* dissolution testing conducted by Amide Pharmaceuticals on its naltrexone HCl 50 mg tablets is acceptable, as gre

2. The sponsor has previously submitted a fasting bioequivalence study on its naltrexone tablet lot #729A2A, comparing it to the reference product REVIA® 50 mg tablet, lot #LD157A, manufactured by Dupont Merck (See Bioequivalency review dated March 27, 1998).

RECOMMENDATIONS

1. The *in vitro* dissolution testing conducted by Amide Pharmaceuticals on its naltrexone HCl 50 mg tablets is acceptable. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of degassed water using USP XXII apparatus II (paddle) at 50 rpm. The dissolution testing should meet the following specifications:

   N[illegible] e
   fo[illegible]

2. The sponsor has previously submitted an acceptable bioequivalence study on its naltrexone HCl 50 mg tablets. Therefore, from the bioequivalence stand point, the firm has met the requirements *in vivo* bioequivalence and *in vitro* dissolution testing.

/S/

Gur J.P. Singh, Ph.D.
Review Branch II, Division of Bioequivalence.

7/16/1998

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: /S/ DATE: 7/21/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence.

GJP SINGH 7/13/98 75274D.498

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

NDA # 75-274 · Applicant Amide Pharmaceutical, Inc.
Drug Naltrexone Hydrochloride Tablets USP
Strength 50 mg

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

REVIEWER:

		DRAFT RECEIPT	FINAL ACTION
1.	Tim Ames, Review Support Br	Date 4/15/99 Initials [illegible]	Date ____ Initials ____

Application Summary:

Original Rec'd date 16 DEC 97
Date Acceptable for Filing Same
Patent Certification (type) P II
Date of Office Bio Review 21 JUL 98
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start ______ End ______
Commitment rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☐
Not Modified Release Dosage form

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 30 MAR 99
Date Patent in effect EXP 1994
Citizens Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
RLD N18932
Pediatric Exclusivity Tracking System
Date checked 15 APR 99
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Comments:

2. Div. Dir./Deputy Dir. (Acting) — Chemistry Div. I or II
Date ______ Initials ______ | Date 4/29/99 Initials M. Smela
Comments: CMC acceptable. Impurity limits are tighter than 1st generic and RLD.

3. Office Level Chem Review (1st Generic Only) — Chemistry Div. I or (II)
Date ______ Initials ______ | Date ______ Initials [illegible] 4/30/99
Comments: NA This is the second generic approval for this drug product.

4. Pat Beers Block RLD = 18932
Supv., Review Support Branch
Date 4/29/99 Initials PmBB | Date 4/29/99 Initials PmBA
Comments:

- EER acceptable for all facilities as of March 30, 1999 (was OAI; [illegible] 4/12/99). March 15, 1999 Consumer Product Testing withdrawn.
- Bioequivalence clinical site/analytical site was AAI Laboratory. Request for inspection history sent to DSI today.

:\wpfile\branch7\ames\apsum.wpd

- Bioequivalence study (single dose, fasting) and dissolution testing was reviewed and found acceptable for approval [illegible]
- Patent information: Firm submitted Para II certification and statement that RLD is not granted marketing exclusivity.
- Finished product labeling for 50 mg Bottles of 30s + 500s was reviewed and found acceptable for approval 4/19/99
- No citizens petitions or controlled correspondence affect this ANDA
- MV - NA/now USP product
- CMC [illegible]

REVIEWER:

		DRAFT RECEIPT	FINAL ACTION
5.	Peter Rickman Supv., Reg. Support Branch Contains certification Yes ☒ No ☐ (required by the GDEA if sub after 6/1/92) Paragraph 4 Certification Yes ☐ No ☐ RLD 18-932 No patent or exclusivity issues Office level Bio (single dose/Fasting) 7/21/98 Comments: 2nd Generic approval EER acceptable 3/30/99 (Verified EES 4/30/99)	Date 4/30/99 Initials [illegible] Determ. of involvement? Yes ☐ No ☒ Pediatric Exclusivity Tracking System Date Checked N/A 4/30/99 RW Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐	Date 4/30/99 Initials [illegible]
6.	~~Jerry Phillips~~ Dir. Div. Labeling & Prog. Support Comments: Acceptable EES dated 3/30/99 (verified 4/30/99). No OAI Alerts. Bioequivalence review (fasting + dissolution) found acceptable 7/16/98. Office level bio endorsed 7/21/98 (D. Conner). Bio study conducted at AAI Clinic, Chapel Hill, NC. CMC acceptable 4/26/99. Methods validation waived. DSI to audit AAI-[illegible] to memo dated 4/26/99 to proceed with approval. Recommend Approve	Date 4/30/99 Initials RW	Date 4/30/99 Initials [illegible] 5/26/99 RW
7.	~~Gordon Johnston~~ Deputy Director, OGD Patent Cert - P_4 Yes ☐ No ☒ Pend. Legal Action Yes ☐ No ☒ Comments: No controlled correspondence or Citizens Petitions currently pending. No pediatric study implications under FDAMA. O.K to approve.	Date 4/30/99 Initials RW Petition Status None No patents or exclusivities currently listed.	Date 4/30/99 Initials [illegible] for
8.	Doug Sporn Dir., OGD Comments:	Date 5/26/99 Initials DLS	Date 5/26/99 Initials DLS
	~~Roger Williams, M.D.~~ ~~Dep.Dir., CDER~~ First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐	Date ______ Initials ______	Date ______ Initials ______
9.	Tim Ames Review Support Branch	Date [signature] Initials 5/27/99	Date ______ Initials ______

RW MH Pediatric Exclusivity Tracking System (check just prior to notification to firm)

5/27/99 Applicant notification:

2:43p Time notified of approval by phone 2:47p Time approval letter faxed

FDA Notification:

5/27/99 Date e-mail message sent to "OGD approvals" account

5/27/99 Date Approval letter copied to "//cder/drugapp" directory

Verified 4/30/99 Rivett

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75274/000**
Stamp: **16-DEC-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority:
Org Code: **600**
Action Goal:
District Goal: **16-FEB-1999**
Brand Name:
Established Name: **NALTREXONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **50 MG**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
V. VENKATARAM (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 30-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 17-APR-1998 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 25-FEB-1998 by J. SINGER (HFD-324) 301-827-0066

Establishment:

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

No:
. No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**

Reason: **BASED ON FILE REVIEW**

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 75-274 **SPONSOR:** Amide
DOSAGE FORM: Naltrexone HCl tablets,
STRENGTHS(s): 50 mg
TYPE OF STUDY: Single dose. Fasting Study
STUDY SITE:

STUDY SUMMARY: Bioequivalence study on naltrexone 50 mg tablets is acceptable.

DISSOLUTION: Dissolution testing on naltrexone 50 mg tablets meets Agency specifications.

WAIVER REQUESTS: NA

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL: _____ DATE 7-13-98

TEAM LEADER: Shriniwas G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: _____ **DATE** 7/16/1998

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: _____ **DATE** 7/21/98

DIRECTOR, OFFICE OF GENERIC DRUGS: Douglas Sporn

INITIAL: _____ DATE _____

DIVISION REVIEW SUMMARY

ANDA: 75-274

FIRM: Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

DOSAGE FORM: Tablet STRENGTH: 50 mg

DRUG: Naltrexone Hydrochloride

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable as of 03/30/1999.

BIO STUDY INFORMATION: Acceptable as of 07/13/98.

METHODS VALIDATION: N/A; compendial articles.

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

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in both container sizes. The container closure for the 30 count package has been changed to a CRC in accordance with Poison Prevention Act and RLD package. The metal cap retains the same innerseal PS-22.

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

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

Description:	Yellow film coated capsule-shaped tablet debossed "A105" on the bisected side.
Assay:	90.0% - 110.0%
Dissolution:	
Related Substances:	
Noroxymorphone:	
N-(3-Butenyl) noroxymorphone (NBN	
2,2'-Bisnaltrexone	
Individual unknown	
Total related substances (known + unknown)	

LABELING: ~~Need final approval worksheet~~. AC 4/19/99

STERILIZATION VALIDATION: N/A

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

OK; found adequate 3/2/99

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

Acceptable. Batch 7292A was tablets. Meets PPG 23-90 10X rule.

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

The proposed production batch sizes are and tablets. Blank batch records are included for each of the proposed batch sizes. A description of the equipment is included and the formulations appear to be correct and accurate for each of the batch sizes.

RECOMMENDATION: APPROVABLE.

SIGNATURE:

A Langowski 4/12/99

Chemist: A. Langowski DATE: 3/31/99

Team Leader: Ubrani V. Venkataram DATE: 4/12/99

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

ANDA Number: **75-274** Date of Submission: **April 14, 1999**

Applicant's Name: **Amide Pharmaceutical, Inc**

Established Name: **Naltrexone Hydrochloride Tablets USP, 50 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 and 500s
Satisfactory as of April 14, 1999 submission.

Professional Package Insert Labeling:
Satisfactory as of April 14, 1999 submission.

Revisions needed post-approval: PI - D&A (Alternative Dosing Schedules) - First paragraph, last sentence - "extended" rather than "extenuated"; place USP with the established name - container and PI - add '77°F) to the storage recommendations; ADVERSE REACTIONS, Opioid Addiction, Laboratory Tests - Relocate last paragraph to be last paragraph in the preceding subsection (Post-marketing Experience).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Revia™

NDA Number: 18-932

NDA Drug Name: Revia™ (Naltrexone Hydrochloride) Tablets

NDA Firm: Dupont Merck

Date of Approval of NDA Insert and supplement #: 3/5/99 (S-014)

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

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? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
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? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does NLD 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 NLD and applicant (page #) in the FTR			
Is the scoring configuration different than the NLD?		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 gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			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? NO - but see FTR. If so, is NDA and/or ANDA in a light resistant container? Both container sizes (30s and 500s) are of HDPE		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: (portions taken from previous review_

1. This review is based on the labeling for Revia™ (Dupont, revised 3/97). Approved 3/5/99. The approved labeling for BARR's ANDA 74-918 (app. 5/8/98) was also used as a guide.
2. Storage/dispensing conditions

ANDA - CONTAINER: Store at 25°C, with brief excursions permitted between 15° and 30°C (59° and 86°F) controlled room temperature, see USP. Dispense in a tight container as defined in the USP.

INSERT: same as the container

NDA - CONTAINER: Store at 25°C with brief excursions permitted between 15° and 30°C (59° and 86°F) controlled room temperature, see USP.

INSERT: Protect from light. (Rev 1/95)

[N.B. - Amide has submitted a PI (Rev 3/97) and a container label for the RLD which do not have the statement "Protect from light" on either one. The RLD container label is the same as above. After consulting with the chemist, D. Shostak, I decided not to ask the firm to put "Protect from light" on any labeling pieces. The containers are of HDPE]

3. Not a USP item. Proposed in PF as - Naltrexone Hydrochloride Tablets.

4. Revia is marketed in bottles of 30s (CRC), 100s and UD 28s. Amide proposes to market container sizes of 30s and 500s (the 30s have CRC).

5. Both Revia™ and Amide's tablets are scored.

6. Amide is the manufacturer.

7. The tablet description as seen in the HOW SUPPLIED section is accurate.

8. The inactives listed in the DESCRIPTION section are correct.

9. This review was done with the red jacket.

Date of Review: 4-16-99 Date of Submission: 4-14-99

Primary Reviewer: Adolph Vezza Date:

Team Leader: Charlie Hoppes Date: 4/19/99

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cc:

P.L.DOC

RECORD OF TELEPHONE CONVERSATION

I spoke to Jasmine Shah today about ANDA 75-274, specifically the 4-12-99 amendment. We has asked the firm to revise their PI to be the same as the recently revised RLD. I did a review on the AMIDE's new PI and found some minor errors. It seems the innovator has changed their storage recommendations. AMIDE made this change in their PI but they did not make it for their container labels. I called to make them aware of this. I also mentioned the minor errors in the PI. Mr. Shah stated that he would just as soon make the PI changes now so I related them to him over the phone. He said that the new PIs and container labels would take about 3 days to do.

Div. of Labeling and Program Support

DATE
April 13, 1999

ANDA NUMBER
75-274

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X **MADE BY TELE.**

X **FDA** _ **IN PERSON**

PRODUCT NAME
Naltrexone Tabs

FIRM NAME
AMIDE

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jasmine Shah
Dir.Reg.Affairs

TELEPHONE NUMBER
(973) 890-1440

SIGNATURE
Adolph Vezza

19

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

ANDA Number: **75-274** Date of Submission: **November 24, 1998**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets USP, 50 mg**

Labeling Deficiencies:

CONTAINER (30s)

We note that you have not responded to the following comment made in the last labeling deficiency letter dated September 24, 1998. Please respond.

The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). You have proposed a container of 30 which appears to be in this category. We note that the listed drug is marketed in bottles of 30 with child-resistant closures. Therefore, we believe that this package must comply with the Act. Please comment.

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTE TO CHEMIST (The message has been forwarded to chemist, Andrew Langowski on 2/12/99)

a. **The firm is required to propose a CRC for 30's based on the "Poison Prevention Acts". The firm appears to have proposed a NON-CRC for their 30's container. Please see the comment under CONTAINER (75274na2.1) and follow up on this issue.**

b. **The firm stated in their amendment dated November 24, 1998 that their final product is yellow whereas the firm's Controls for Finished Dosage Form indicates as white. Is this a chemistry issue to be addressed?**

c. **Please note that this product is now a subject of USP monograph. Refer to USP supplement #9.**

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 30s and 500s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Revia™

NDA Number: 18-932

NDA Drug Name: Revia™ (Naltrexone Hydrochloride) Tablets

NDA Firm: Dupont Merck

Date of Approval of NDA Insert and supplement #: 12/30/94 (S-010)

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

FOR THE RECORD: (From the previous record with modification)

1. This review is based on the labeling for Revia™ (Dupont, revised 1/95). Acknowledge and retain 3/4/96. The approved labeling for BARR's ANDA 74-918 (app. 5/8/98) was also used as a guide.

2. The label sand labeling submitted on 11/24/98 appear to be acceptable for approval. However, see the comment under CONTAINER and FTR #3 for post-approval revision required.

3. We will ask the following changes as a Post-approval revision.

   a. GENERAL

      Please note that this drug product is now the subject of a USP monograph titled "Naltrexone Hydrochloride Tablets USP". We refer you to USP 23/Supplement #9. Therefore, at the time of next printing revise all labels and labeling accordingly.

   b. DESCRIPTION

      i. Second paragraph:

         ... 314-dihydroxymorphinan-6-... [no hyphen after "dihydroxy"]

      ii. We encourage you to alphabetize the listing of inactive ingredients.

   c. DOSAGE AND ADMINISTRATION (Alternative Dosing Schedules) - First paragraph, last sentence:

      ...these extended dosing... [rather than "extenuated"]

   d. HOW SUPPLIED

      We ask that you relocate the last two paragraphs appearing in the DOSAGE AND ADMINISTRATION section to this section.

4. Storage/dispensing conditions

   ANDA - CONTAINER: Store at controlled room temperature 15°-30°C (59°-86°F) [I have asked the firm to revise "-" to read "to".]

   Dispense in a tight container as defined

in the USP.

INSERT: No comments - I have asked them to include the information as seen on the container label

NDA - CONTAINER: Store at controlled room temperature 15°-30°C (59°-86°F).

INSERT: Protect from light. (Rev 1/95)

[N.B. - Amide has submitted a PI (Rev 10/95) and a container label for the RLD which do not have the statement "Protect from light" on either one. The RLD container label is the same as above. After consulting with the chemist, D. Shostak, I decided not to ask the firm to put "Protect from light" on any labeling pieces. The containers are of HDPE. The USP labeling does not require "Protect from light."]

5. This drug product is now a subject of USP monograph. (Supplement #9)

6. Revia is marketed in bottles of 30s (CRC), 100s and UD 28s. Amide proposes to market container sizes of 30s and 500s (neither with CRC). I have asked Amide to consider using CRCs for their 30s container size.

7. Both Revia™ and Amide's tablets are scored.

8. Amide is the sole manufacturer.

9. According to the firm's response dated November 24, 1998, their final product is yellow and hence accurately described in the H.S. section.

10. The inactives listed in the DESCRIPTION section are correct.

Date of Review: 1/14/99 Date of Submission: 11/24/98

Primary Reviewer: Chan park /S/ Date: 2/12/99

Team Leader: Charlie Hoppes Date:

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cc: /S/ 2/12/99

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

ANDA Number: 75-274 Date of Submission: **November 24, 1998**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **, Naltrexone Hydrochloride Tablets USP, 50 mg**

Labeling Deficiencies:

CONTAINER (30s)

We note that you have not responded to the following comment made in the last labeling deficiency letter dated September 24, 1998. Please respond.

The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). You have proposed a container of 30 which appears to be in this category. We note that the listed drug is marketed in bottles of 30 with child-resistant closures. Therefore, we believe that this package must comply with the Act. Please comment.

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.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: **75-274** Date of Submission: **December 15, 1997**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets, 50 mg**

Labeling Deficiencies:

1. GENERAL COMMENT:

   As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER 30s and 500s

   a. See GENERAL COMMENT above.

   b. "**Usual Adult Dosage:**" rather than "**Dosage:**".

   c. Store at controlled room temperature 15° to 30°C (59° to 86°C). ("to" instead of hyphen)

   d. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). You have proposed a container of 30 which appears to be in this category. We note that the listed drug is marketed in bottles of 30 with child-resistant closures. Therefore, we believe that this package must comply with the Act. Please comment.

3. INSERT

a. GENERAL COMMENTS

i. There is no need to capitalize the established name throughout the text of the insert unless required by sentence structure.

ii. Replace the hyphen with the word "to" when stating a range of values (e.g., 30 to 127 mL/min).

iii. Replace the proprietary name "Narcan®" with "naloxone" throughout the text of the insert except where otherwise directed.

iv. Include a space between the numerical unit and its qualifier throughout the text of the insert (e.g.; "50 mg" rather than "50mg").

v. Please be consistent in your format for section, subsection, and sub-subsection headings throughout your insert (e.g.; **DOSAGE AND ADMINISTRATION:**, **Treatment of Narcotic Dependence:**, *Initiate treatment with naltrexone using the following guidelines:*, Naloxone Challenge Test: Intravenous challenge:).

b. DESCRIPTION

i. Please include the chemical name (second USP name), molecular formula and molecular weight in this section.

ii. See GENERAL COMMENT 3(a)(iii) above.

iii. Please add "The structural formula is as follows:" immediately before the structural formula.

iv. Second paragraph - Revise the last sentence as follows:

Naltrexone hydrochloride tablets, for oral administration, are ...

v. Last paragraph

A). "anhydrous lactose" rather than "lactose".

B). Include "colloidal silicon dioxide" as well as "silicon dioxide" in your listing of inactive ingredients.

C). Also include titanium dioxide in your listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamic Actions

A). Capitalize the "A" in "Actions".

B). Delete the word "hydrochloride" except in the first sentence and in the fourth paragraph ("Clinical studies ...).

C). Fifth paragraph ("Naltrexone blocks the ..."), first sentence - ... analogous to ... [delete the ")"].

ii. Pharmacokinetics - Delete the word "hydrochloride".

iii. Clinical Trials

A). Place the subsection titles in this subsection in *italic* print.

B). *Alcoholism*

1). Delete "hydrochloride" except in the second sentence (first paragraph and second paragraph).

2). First paragraph, second sentence - ... as an adjunct ... (add word "an").

3). Second paragraph, third sentence - ... 82 alcohol-dependent patients ... (add hyphen).

C). *Treatment of narcotic addiction* - Delete the word "hydrochloride".

D). *Individualization of dosage*

1). Delete the word "hydrochloride".

2). "OPIOID" (spelling)

E). *Treatment of alcoholism*

1). Delete the word "hydrochloride".

2). First paragraph, last sentence - "durations" (plural).

F). *Treatment of narcotic dependence*

1). First sentence - ... of parenterally ... (delete the word "the").

2). Delete "hydrochloride" in the first sentence of the first paragraph and the last sentence in the second paragraph.

3). Last sentence - ... (see **PRECAUTIONS: Information for Patients:**).

d. INDICATIONS AND USAGE

i. First sentence - Naltrexone hydrochloride tablets are indicated in the ...

ii. Second paragraph - Delete "hydrochloride".

e. CONTRAINDICATIONS

i. Delete "hydrochloride" throughout this section.

ii. "Naltrexone is ..." (Delete the bold print).

f. WARNINGS

i. Hepatotoxicity

A). Delete "hydrochloride" throughout this subsection except in the second occurrence in the paragraph beginning "Evidence of ..." and both instances in

the paragraph beginning "The conclusion is ..."

B). Last sentence of paragraph beginning "Evidence of ..." - ... is a direct ... (add "a").

ii. Unintended Precipitation of Abstinence

A). Delete "hydrochloride tablets" from the first paragraph (2 instances) and "hydrochloride" from the remainder of the subsection.

B). Last paragraph

1). First sentence - ... respiratory arrest, circulatory collapse). (delete "and").

2). (See **PRECAUTIONS: Information for Patients:**.)

g. PRECAUTIONS

i. General

A). **"General"** is a subsection title and should be printed in a format consistent with other subsection headings.

B). "*When reversal of naltrexone blockade is required*" and "*When withdrawal is accidentally precipitated with naltrexone*" and "*Suicide*" are subsections of the "General" subsection and their titles should appear in a format consistent with other subsection headings.

C). Note the deletion of the word "Hydrochloride" in the subsection titles.

D). Delete "hydrochloride" thrbughout this subsection.

ii. Information for Patients - Delete "hydrochloride" throughout this subsection except in the first sentence of the second

paragraph which should read ... prescribed naltrexone hydrochloride tablets as part ...

iii. Laboratory Tests

A). Capital "T" in "Tests".

B). Delete "hydrochloride" throughout this subsection.

C). Second paragraph, first sentence - ... high pressure ... (delete hyphen).

iv. Drug Interactions - Delete "hydrochloride" throughout this subsection.

v. Carcinogenesis, Mutagenesis, Impairment of Fertility

A). This is a subsection and its title should appear in bold lower-case print.

B). Replace the "AND" in the title with a comma.

C). "*Carcinogenesis*", "*Mutagenesis*", and "*Impairment of fertility*" are subsections of the "**Carcinogenesis, Mutagenesis, Impairment of Fertility**" subsection and their titles should be italic print.

D). Carcinogenesis, first sentence - "numbers" (plural).

vi. **Pregnancy**: Category C

A). Delete the bold print in "Category C".

B). Delete "hydrochloride" in the first instance in the first paragraph and in the last paragraph.

vii. "**Labor and Delivery**", "**Nursing Mothers**", and "**Pediatric Use**" are subsection titles and should appear in a format consistent with other subsection headings.

A). Labor and Delivery - Delete "hydrochloride".

B). Nursing Mothers

1). Whether or not naltrexone is ...

2). Delete "hydrochloride".

C). Pediatric Use - Delete "hydrochloride".

h. ADVERSE REACTIONS

i. Delete "hydrochloride" throughout this section except the third instance in the first paragraph and the third instance in the second paragraph.

ii. Second paragraph - ... **WARNINGS** and **PRECAUTIONS** ... (word "and" in lower case and unbolded).

iii. Paragraph beginning "Among opioid free ...", last paragraph, last sentence - ... **WARNINGS**, and **DOSAGE** ... (add "and").

iv. Reported Adverse Events:

A). Add colon to subsection title.

B). Delete "hydrochloride".

C). (see **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

v. Alcoholism - Delete "hydrochloride".

vi. Narcotic Addiction

A). Delete "hydrochloride".

B). Incidence rate more than 10% - ... low energy, joint and ... (add comma).

C). Less than 1%

1). Special Senses - ... ears- "clogged", aching ... (note quotation marks).

2). Other - "Depression" rather than "Depressing"

i. DRUG ABUSE AND DEPENDENCE

Delete "hydrochloride".

j. OVERDOSAGE

i. Delete "hydrochloride".

ii. "800 mg" (delete hyphen).

k. DOSAGE AND ADMINISTRATION

i. Delete "HYDROCHLORIDE" from the first sentence.

ii. Treatment of Alcoholism:

A). Add colon to subsection heading.

B). Delete "hydrochloride".

C). First sentence - (see **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

iii. Treatment of Narcotic Dependence:

A). Add colon to subsection heading.

B). *Initiate treatment with naltrexone using the following guidelines:*.

1). This is a sub subsection title and should be in *italic* print.

2). Delete "hydrochloride" in the title.

3). Naloxone Challenge Test

a). Intravenous challenge

i). "naloxone hydrochloride" rather than "naloxone".

ii). last sentence - ... remaining 0.6 mg of ...

b). Subcutaneous challenge - ... If the subcutaneous ... (add "the")

c). Interpretation of the challenge

i). Lower case "c"

ii). Delete "hydrochloride".

iii). "Warning:" rather than "Warnings:"

iv. Alternative Dosing Schedules

A). "Alternative" rather than "Alternate".

B). First paragraph

1). Penultimate sentence - ... naltrexone hydrochloride every weekday ... (delete "should").

2). Last sentence - Delete "hydrochloride".

C). Second paragraph - (see **WARNINGS** and **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

D). Patient Compliance - Delete "hydrochloride".

1. HOW SUPPLIED

i. Naltrexone hydrochloride tablets 50 mg are ...

ii. Tablet description

A). We note that you have described your tablet as "yellow" yet reference is made to a "white" tablet on pages 1355 and 1360. Please comment and/or revise.

B). ... capsule-shaped tablet ...

iii. Include the following statements:

A). "Rx only" or "℞ only". [see GENERAL COMMENT (1)]

B). Store at controlled room temperature 15° to 30°C (59° to 86°C).

C). Dispense in a tight container as defined in the USP.

iv. We encourage you to use the NDC number in this section.

v. Revise your name and address to be the same as that seen on your container labels.

Please revise your container labels and insert labeling, as instructed above, and submit final printed container labels and final printed (or draft, if you prefer) insert labeling.

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.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

file in ANDA 75-274
cc: (Amide Letter)

Date MAY 12 1998

From Consumer Safety Officer
Investigations & Preapproval Compliance Br/DMPQ (HFD-324)

Subject Acceptable Recommendation
Carisoprodol, Aspirin and Codeine Phosphate Tablets
(ANDA 40-283)

To Patricia M. Beers-Block
Office of Generic Drugs (HFD-617)

Firm: Amide Pharmaceuticals Inc
101 East Main Street
Little Falls, NJ 07424
CFN #2244683

We have completed our review of the Establishment Inspection Report (EIR) for Amide Pharmaceuticals located at 101 East Main Street, Little Falls, NJ 07424. The facility was inspected by the FDA New Jersey District Office (NWJ-DO) from April 2-15, 1998. At the conclusion of the inspection, NWJ-DO recommended withholding approval of ANDA 40-283 due to inadequate development data for establishing specifications for tablet hardness, thickness and weight.

On April 15, 1998, at the close-out meeting, the firm indicated that the current tablet specifications would be evaluated and revised, if necessary, based on data generated by the firm. In the future, the firm will utilize R&D data to establish tablet specifications.

The Division of Manufacturing and Product Quality (DMPQ) has reviewed the EIR and finds that Amide Pharmaceuticals is acceptable as the manufacturing site for the finished dosage form for ANDA 40-283.

A copy of the EIR is attached for your review.

If you have any questions please contact me at (301) 827-0066.

John M. Singer

John M. Singer

Attachment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75274/000**
Stamp: **16-DEC-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority: Org Code: **600**
Action Goal: District Goal: **16-FEB-1999**
Brand Name:
Established Name: **NALTREXONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **50 MG**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
U. VENKATARAM (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 30-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 17-APR-1998 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 25-FEB-1998 by J. SINGER (HFD-324) 301-827-0066

Establishment: **2244683**
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-MAR-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**

Reason: **BASED ON FILE REVIEW**

Memorandum

Date FEB 25 1998

From Consumer Safety Officer
Investigations & Preapproval Compliance Br/DMPQ (HFD-324)

Subject Recommendation to Withhold Approval
Naltrexone Hydrochloride Tablets (ANDA 75-274) Br 6
Oxycodone/Acetaminophen Tablets (ANDA 40-203) Br 6
Digoxin Tablets (ANDA 40-282) Br 6
Carisoprodol/Aspirin/Codeine Phosphate Tablets (ANDA 40-283) Br 2

To Gordon R. Johnston
Office of Generic Drugs (HFD-601)

Applicant/Firm: Amide Pharmaceutical, Inc
101 East Main Street
Little Falls, NJ 07424
CFN #2244683

We have completed our review of the Establishment Inspection Report (EIR) for Amide Pharmaceutical, Inc located at 101 East Main Street, Little Falls, NJ 07424. The facility was inspected by the FDA New Jersey District Office (NWJ-DO) from November 4 to December 1, 1997.

NWJ-DO conducted a CGMP inspection at the request of the NWJ-DO Compliance Branch to determine if the firm's request for relief from the Consent Decree of Permanent Injunction (signed 3-23-92) should be granted.

During the inspection, NWJ-DO observed many significant CGMP violations that affect the firm's entire operation. Following the inspection, NWJ-DO recommended that the firm remain under the Consent Decree, and that approval of ANDA 75-274 be withheld. On December 24, 1997, NWJ-DO also recommended that other pending applications be withheld due to many significant CGMP violations.

The Division of Manufacturing and Product Quality (DMPQ) concurs with the District's recommendation to withhold approval of ANDA 75-274, ANDA 40-203, ANDA 40-282 and ANDA 40-283. Significant CGMP deficiencies noted during the inspection **include but are not limited to** the following:

1. Impurity profile testing has not been conducted/completed for 25 active pharmaceutical ingredients.

2. Storage areas for active pharmaceutical ingredients and excipients are not monitored for temperature and humidity.

3. The quality control laboratory has established a 12 month expiration dating period for all in-house reference standards. However, no stability studies have been conducted to support the expiration dating periods.

4. The quality control laboratory utilizes 11 ----- for data collection. However, the firm cannot assure the integrity of the HPLC data due to the lack of an audit trail.

5. The firm's cleaning validation studies for ANDA drug products only utilized 1 batch of drug product per study. Cleaning validation studies should have been conducted utilizing 3 consecutive batches per study.

6. The firm lacks a written SOP detailing the water sampling procedure for both routine sampling and for use in manufacturing. In addition, the firm lacks data to support the general maintenance and testing requirements for the following areas of the purified water system: two filters, the carbon beds, and the UV light.

A copy of the EIR is attached for your review.

If you have any questions please contact me at (301) 827-0071.

John M. Singer

John M. Singer

Attachment

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

ANDA Number: **75-274** Date of Submission: **December 15, 1997**

Applicant's Name: **Amide Pharmaceutical, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets, 50 mg**

Labeling Deficiencies:

1. GENERAL COMMENT:

   As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "℞ only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER 30s and 500s

   a. See GENERAL COMMENT above.

   b. "**Usual Adult Dosage:**" rather than "**Dosage:**".

   c. Store at controlled room temperature 15° to 30°C (59° to 86°C). ("to" instead of hyphen)

   d. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). You have proposed a container of 30 which appears to be in this category. We note that the listed drug is marketed in bottles of 30 with child-resistant closures. Therefore, we believe that this package must comply with the Act. Please comment.

3. INSERT

a. GENERAL COMMENTS

i. There is no need to capitalize the established name throughout the text of the insert unless required by sentence structure.

ii. Replace the hyphen with the word "to" when stating a range of values (e.g., 30 to 127 mL/min).

iii. Replace the proprietary name "Narcan®" with "naloxone" throughout the text of the insert except where otherwise directed.

iv. Include a space between the numerical unit and its qualifier throughout the text of the insert (e.g.; "50 mg" rather than "50mg").

v. Please be consistent in your format for section, subsection, and sub-subsection headings throughout your insert (e.g.; **DOSAGE AND ADMINISTRATION:**, **Treatment of Narcotic Dependence:**, *Initiate treatment with naltrexone using the following guidelines:*, Naloxone Challenge Test: Intravenous challenge:).

b. DESCRIPTION

i. Please include the chemical name (second USP name), molecular formula and molecular weight in this section.

ii. See GENERAL COMMENT 3(a)(iii) above.

iii. Please add "The structural formula is as follows:" immediately before the structural formula.

iv. Second paragraph - Revise the last sentence as follows:

Naltrexone hydrochloride tablets, for oral administration, are ...

v. Last paragraph

A). "anhydrous lactose" rather than "lactose".

B). Include "colloidal silicon dioxide" as well as "silicon dioxide" in your listing of inactive ingredients.

C). Also include titanium dioxide in your listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamic Actions

A). Capitalize the "A" in "Actions".

B). Delete the word "hydrochloride" except in the first sentence and in the fourth paragraph ("Clinical studies ...).

C). Fifth paragraph ("Naltrexone blocks the ..."), first sentence - ... analogous to ... [delete the ")"].

ii. Pharmacokinetics - Delete the word "hydrochloride".

iii. Clinical Trials

A). Place the subsection titles in this subsection in *italic* print.

B). *Alcoholism*

1). Delete "hydrochloride" except in the second sentence (first paragraph and second paragraph).

2). First paragraph, second sentence - ... as an adjunct ... (add word "an").

3). Second paragraph, third sentence - ... 82 alcohol-dependent patients ... (add hyphen).

C). *Treatment of narcotic addiction* - Delete the word "hydrochloride".

D). *Individualization of dosage*

1). Delete the word "hydrochloride".

2). "OPIOID" (spelling)

E). *Treatment of alcoholism*

1). Delete the word "hydrochloride".

2). First paragraph, last sentence - "durations" (plural).

F). *Treatment of narcotic dependence*

1). First sentence - ... of parenterally ... (delete the word "the").

2). Delete "hydrochloride" in the first sentence of the first paragraph and the last sentence in the second paragraph.

3). Last sentence - ... (see **PRECAUTIONS: Information for Patients:**).

d. INDICATIONS AND USAGE

i. First sentence - Naltrexone hydrochloride tablets are indicated in the ...

ii. Second paragraph - Delete "hydrochloride".

e. CONTRAINDICATIONS

i. Delete "hydrochloride" throughout this section.

ii. "Naltrexone is ..." (Delete the bold print).

f. WARNINGS

i. Hepatotoxicity

A). Delete "hydrochloride" throughout this subsection except in the second occurrence in the paragraph beginning "Evidence of ..." and both instances in

the paragraph beginning "The conclusion is ..."

B). Last sentence of paragraph beginning "Evidence of ..." - ... is a direct ... (add "a").

ii. Unintended Precipitation of Abstinence

A). Delete "hydrochloride tablets" from the first paragraph (2 instances) and "hydrochloride" from the remainder of the subsection.

B). Last paragraph

1). First sentence - ... respiratory arrest, circulatory collapse). (delete "and").

2). (See **PRECAUTIONS: Information for Patients:.**)

g. PRECAUTIONS

i. General

A). "**General**" is a subsection title and should be printed in a format consistent with other subsection headings.

B). "*When reversal of naltrexone blockade is required*" and "*When withdrawal is accidentally precipitated with naltrexone*" and "*Suicide*" are subsections of the "General" subsection and their titles should appear in a format consistent with other subsection headings.

C). Note the deletion of the word "Hydrochloride" in the subsection titles.

D). Delete "hydrochloride" throughout this subsection.

ii. Information for Patients - Delete "hydrochloride" throughout this subsection except in the first sentence of the second

paragraph which should read ... prescribed naltrexone hydrochloride tablets as part ...

iii. Laboratory Tests

A). Capital "T" in "Tests".

B). Delete "hydrochloride" throughout this subsection.

C). Second paragraph, first sentence - ... high pressure ... (delete hyphen).

iv. Drug Interactions - Delete "hydrochloride" throughout this subsection.

v. Carcinogenesis, Mutagenesis, Impairment of Fertility

A). This is a subsection and its title should appear in bold lower-case print.

B). Replace the "AND" in the title with a comma.

C). "*Carcinogenesis*", "*Mutagenesis*", and "*Impairment of fertility*" are subsections of the "**Carcinogenesis, Mutagenesis, Impairment of Fertility**" subsection and their titles should be italic print.

D). Carcinogenesis, first sentence - "numbers" (plural).

vi. **Pregnancy**: Category C

A). Delete the bold print in "Category C".

B). Delete "hydrochloride" in the first instance in the first paragraph and in the last paragraph.

vii. "**Labor and Delivery**", "**Nursing Mothers**", and "**Pediatric Use**" are subsection titles and should appear in a format consistent with other subsection headings.

A). Labor and Delivery - Delete "hydrochloride".

B). Nursing Mothers

1). Whether or not naltrexone is ...

2). Delete "hydrochloride".

C). Pediatric Use - Delete "hydrochloride".

h. ADVERSE REACTIONS

i. Delete "hydrochloride" throughout this section except the third instance in the first paragraph and the third instance in the second paragraph.

ii. Second paragraph - ... **WARNINGS** and **PRECAUTIONS** ... (word "and" in lower case and unbolded).

iii. Paragraph beginning "Among opioid free ...", last paragraph, last sentence - ... **WARNINGS**, and **DOSAGE** ... (add "and").

iv. Reported Adverse Events:

A). Add colon to subsection title.

B). Delete "hydrochloride".

C). (see **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

v. Alcoholism - Delete "hydrochloride".

vi. Narcotic Addiction

A). Delete "hydrochloride".

B). Incidence rate more than 10% - ... low energy, joint and ... (add comma).

C). Less than 1%

1). Special Senses - ... ears- "clogged", aching ... (note quotation marks).

2). Other - "Depression" rather than "Depressing"

i. DRUG ABUSE AND DEPENDENCE

Delete "hydrochloride".

j. OVERDOSAGE

i. Delete "hydrochloride".

ii. "800 mg" (delete hyphen).

k. DOSAGE AND ADMINISTRATION

i. Delete "HYDROCHLORIDE" from the first sentence.

ii. Treatment of Alcoholism:

A). Add colon to subsection heading.

B). Delete "hydrochloride".

C). First sentence - (see **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

iii. Treatment of Narcotic Dependence:

A). Add colon to subsection heading.

B). *Initiate treatment with naltrexone using the following guidelines:.*

1). This is a sub subsection title and should be in *italic* print.

2). Delete "hydrochloride" in the title.

3). Naloxone Challenge Test

a). Intravenous challenge

i). "naloxone hydrochloride" rather than "naloxone".

ii). last sentence - ... remaining 0.6 mg of ...

b). Subcutaneous challenge - ... If the subcutaneous ... (add "the")

c). Interpretation of the challenge

i). Lower case "c"

ii). Delete "hydrochloride".

iii). "Warning:" rather than "Warnings:"

iv. Alternative Dosing Schedules

A). "Alternative" rather than "Alternate".

B). First paragraph

1). Penultimate sentence - ... naltrexone hydrochloride every weekday ... (delete "should").

2). Last sentence - Delete "hydrochloride".

C). Second paragraph - (see **WARNINGS** and **CLINICAL PHARMACOLOGY, Clinical Trials,** *Individualization of dosage*).

D). Patient Compliance - Delete "hydrochloride".

1. HOW SUPPLIED

i. Naltrexone hydrochloride tablets 50 mg are ...

ii. Tablet description

A). We note that you have described your tablet as "yellow" yet reference is made to a "white" tablet on pages 1355 and 1360. Please comment and/or revise.

B). ... capsule-shaped tablet ...

iii. Include the following statements:

A). "Rx only" or "℞ only". [see GENERAL COMMENT (1)]

B). Store at controlled room temperature 15° to 30°C (59° to 86°C).

C). Dispense in a tight container as defined in the USP.

iv. We encourage you to use the NDC number in this section.

v. Revise your name and address to be the same as that seen on your container labels.

Please revise your container labels and insert labeling, as instructed above, and submit final printed container labels and final printed (or draft, if you prefer) insert labeling.

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.

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

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 30s and 500s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Revia™

NDA Number: 18-932

NDA Drug Name: Revia™ (Naltrexone Hydrochloride) Tablets

NDA Firm: Dupont Merck

Date of Approval of NDA Insert and supplement #: 12/30/94 (S-010)

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

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 PI?	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? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? YES See comment (2)(d) in review	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? YES - See comments under 3(l)(iv) in review. Is "Jointly Manufactured by...", statement needed? NO	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? YES - See comments under 3(b)(v) in review	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	

	Yes	No	N.A.
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? NO - But see FTR If so, is NDA and/or ANDA in a light resistant container? Both container sizes (30s and 500s) are of HDPE		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, revised 1/95). Acknowledge and retain 3/4/96. The approved labeling for BARR's ANDA 74-918 (app. 5/8/98) was also used as a guide.

2. Storage/dispensing conditions

ANDA - CONTAINER: Store at controlled room temperature 15°-30°C (59°-86°F) [I have asked the firm to revise "-" to read "to".] Dispense in a tight container as defined in the USP.

INSERT: No comments - I have asked them to include the information as seen on the container label

NDA - CONTAINER: Store at controlled room temperature 15°-30°C (59°-86°F).

INSERT: Protect from light. (Rev 1/95)

[N.B. - Amide has submitted a PI (Rev 10/95) and a container label for the RLD which do not have the statement "Protect from light" on either one. The RLD container label is the same as above. After consulting with the chemist, D. Shostak, I decided not to ask the firm to put "Protect from light" on any labeling pieces. The containers are of HDPE]

3. Not a USP item. Proposed in PF as - Naltrexone Hydrochloride Tablets.

4. Revia is marketed in bottles of 30s (CRC), 100s and UD 28s. Amide proposes to market container sizes of 30s and 500s (neither with CRC). I have asked Amide to consider using CRCs for their 30s container size.

5. Both Revia™ and Amide's tablets are scored.

6. Amide is the manufacturer. They have included a street address on their container labels but not in their PI. I asked them to have both manufactured by statements the same as that as seen on the container labels.

7. The tablet description as seen in the HOW SUPPLIED section is not complete and may not be accurate. The tablet is described as "yellow" here but "white" on 2 pages in Amide's submission. The chemist has also noted this in his review. Also, I have asked the firm to include "capsule-shaped" as part of the tablet's description.

8. The inactives listed in the DESCRIPTION section are not entirely correct. The product contains both "silicon dioxide" and "colloidal silicon dioxide" but only mentions "silicon dioxide" in the DESCRIPTION section. They do not list the presence of titanium dioxide in the DESCRIPTION section and they list "lactose" rather than "anhydrous lactose" in this section.

9. This review was done with the red jackets.

Date of Review: 6-8-98 Date of Submission: 12-15-97

Primary Reviewer: Adolph Vezza /S/ Date: 6/9/98

Team Leader: Charlie Hoppes /S/ Date: 6/10/98

---

cc:

CDER Establishment Evaluation Report
for January 12, 1998

Application: **ANDA 75274/000**
Stamp: **16-DEC-1997** Regulatory Due:
Applicant: **AMIDE PHARM**
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

Priority:
Org Code: **600**
Action Goal:
District Goal: **16-FEB-1999**
Brand Name:
Established Name: **NALTREXONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **50 MG**

FDA Contacts: **T. AMES (HFD-617)** **301-827-5849 , Project Manager**
U. VENKATARAM (HFD-647) **301-827-5849 , Team Leader**

Overall Recommendation:

Establishment: **2244683**
AMIDE PHARMACEUTICAL INC
101 EAST MAIN ST
LITTLE FALLS, NJ 07424

DMF No:

AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 12-JAN-1998**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 12-JAN-1998**

Responsibilities:
DRUG SUBSTANCE OTHER TESTER

Establishment:

DMF No:

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC 12-JAN-1998**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Project Manager Tim Ames

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

AADA/ANDA# 75-274 **FIRM NAME** amide

RELATED APPLICATION(S) N/A

DRUG NAME: Naltrexone HCl

DOSAGE FORM: Tablet, 50mg

FIRST GENERIC? N/A

Team Leader Venkataram

Labeling Reviewer adolph Vozza AEV

Random Assignment Random IV

Micro Reviewer N/A

Pharmacodynamic study (Dr. Fanning) N/A

Letter Date 12/15/97 **Received Date** 12/16/97

		YES	NO
	Comments EC1 ✓ On Cards ✓ Therapeutic Code 20 30 400 ✓ narcotic antagonists	✓	
	Methods Validation Package (3 copies) ✓ (Required for Non-USP drugs)	✓	
	AADA Monograph	/	
	Archival, and Review copies Field copy certification (original signature)	✓	
	Cover Letter	✓	
	Table of Contents	✓	

Yes NO

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status)	✓	
Sec. II	**Basis for Submission** RLD or Monograph Revia Firm Dupont Is an ANDA suitability petition required? N/A	✓	
Sec. III	**Patent Certification** 1. Paragraph? IV 2. Expiration of Patent ____	✓	
	Exclusivity Statement	✓	
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓	
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓	✓	
Sec. VI	**Bioavailability/Bioequivalence** 1. In Vivo Study Protocol(s) ✓ 2. In Vivo Study(ies) ✓ 3. Computer Disk Submitted ✓ 1.1 (Lot #: Revia LD157A; Naltrexone 7292A) 4. Request for Waiver of In Vivo Study(ies) ____ 5. In Vitro Dissolution Data ✓ 6. Formulation Data Same? (Comparison of all Strengths) ____ (Ophthalmics, Otics, Externals, Parenterals) 7. Paragraph IV bio study acceptable for filing N/A 8. Lot numbers of products used in Bio-study ____ Lot #	✓	
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓	✓	

Yes NO

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ✓ c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s) ✓ d. Applicant certificate of analysis ____ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ____ g. Approved application for bulk antibiotic N/A h. CFN numbers ____ 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' certificates of analysis (specifications and test results) ✓ d. Applicant certificate of analysis ✓	✓	
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing ____ 2. CGMP Certification ✓ 3. CFN numbers 2244683	✓	
Sec. X	**Outside Firms Including Contract Testing Laboratories** ✓ 1. Full Address ____ 2. Functions ____ 3. CGMP Certification/GLP ✓ 4. CFN numbers 2210008 – Liberica Celsis Testing	✓	
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified ____ 3. If sterile product: Aseptic fill N/A / Terminal sterilization ____ 4. Reprocessing Statement ✓	✓	

		Yes	No
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (AADA/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓	
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and supplier's address ✓	✓	
Sec. XIV	**Controls for the Finished Dosage Form** Lot # 7292A 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓	✓	
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ pg 1613-1614 2. Post Approval Commitments ✓ pg 1615 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on Stability records the same as the test batch ✓ Package Size: 30 → Batch # 7292A2; 500 → Batch # 7292A1		
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	✓	
Sec. XVII	**Environmental Impact Analysis Statement**	✓	

4e3 NC

Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])_____ 2. Debarment Certification (original signature) ✓ 3. List of Convictions statement (original signature)_____		

Reviewing CSO/CST DAme **Date** 12/29/97

Recommendation: **FILE** **REFUSE to FILE**

Supervisory Concurrence/Date _____

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD_____for consult

Type of consult:

Comments regarding the ANDA:

RECORD OF TELEPHONE CONVERSATION

Subject: Correct Address Of where Active ingredient, Naltrexone was manufactured.

I called Mr. Shah and requested conformation on the exact address of where the active ingredient, **Naltrexone Hydrochloride** was manufactured. He assured me he will fax me the information immediately and follow with a hard copy.

DATE
1/9/98

APPLICATION NUMBER
ANDA 75-274

IND NUMBER

TELECON

INITIATED BY _ **APPLICANT/ SPONSOR** X_ **FDA**

MADE X_ **BY TELE.** _ **IN PERSON**

PRODUCT NAME
Naltrexone Hydrochloride Tab 50 mg.

FIRM NAME
Amide Pharmaceutical,. Inc

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Jasmine Shah

TELEPHONE NUMBER
(973) 890-1440

SIGNATURE
Denise Huie
1/9/98

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-274

CORRESPONDENCE

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

April 14, 1999

FA

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

LABELING AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to my telephone conversation with Mr. Adolph Vezza, on April 13, 1999 enclosed find response to the labeling deficiency as follows:

Amide has revised the labeling as per our telephone conversation.

The labels has been revised to include the storage conditions as per the insert.

The insert has been revised with the changes as recommended by Mr. Vezza during our telephone conversation.

Enclosed find twelve (12) copies of final printed labels and insert for Amide's Naltrexone Tablets.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
APR 1 [illegible] 1999
GENERIC DRUGS

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

April 12, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

LABELING AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the deficiency letter dated April 1, 1999 enclosed find response to the labeling deficiency as follows:

Amide has revised the labeling as recommended in the deficiency letter. The insert has been revised comparable to the new insert by the reference product along with the deficiencies to the insert for the reference product.

Enclosed find twelve (12) copies of final printed insert for Amide's Naltrexone Tablets.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
APR 1

GENERIC DRUGS

HIGH QUALITY PHARMACEUTICALS

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

March 15, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room - HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

NDA ORIG AMENDMENT
N/FA

FACSIMILE AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the deficiency letter dated March 12, 1999 enclosed find response to the deficiency as follows:

CHEMISTRY DEFICIENCY

1. Regarding the component and composition statements, the requested quantitative listing could not be found. We acknowledge a quantitative listing as part of the batch record, however, please note that we require that a separate quantitative listing of the component and composition be submitted in Section VII of the application.

   In addition, we request that you add Talc, USP to the qualitative listing of the components and composition as it is also used in the manufacturing process.

Response: Enclosed is a copy of the Component and Composition page in Attachment I.

2. It was indicated that you initially purchased the reference standard from and that it was analyzed for potency by titration and identification by IR spectroscopy. However the IR Spectra provided were of a standard labeled ca.

   Considering the confusion of the source of the standard and the poor quality of IR spectral scan, request that you resubmit IR spectra of the USP reference standard versus the lot of active ingredient used in the test batch.

Response: The reference standard used during the initial IR test was in-fact manufactured by

Attached in Attachment II, is a copy of the IR spectra for the USP reference standard versus the lot used in the test batch (PO# 8218)

3. We acknowledge your commitment to reduce the release and stability limit for impurities. However the specification sheet which indicated the revised stability limits was not found in your amendment. Please submit a copy of your revised stability specification document.

Response: Attached in attachment III, is a copy of the revised specification for the stability test.

4. Please note that although your analytical methods are deemed acceptable as alternate analytical procedures, we still require a commitment acknowledging the USP monograph methods as the official regulatory methods. In case of a dispute concerning violative samples, the results obtained by the USP method will take precedence.

Response: Attached in Attachment IV, is a signed copy of the commitment as requested.

5. Please refer to the labeling comment regarding the Poison Prevention Packaging Act as it relates to the container closure. We request a Child Resistant Closure be utilized in the 30 count packaging configuration. Please note that if a substantially different closure is employed, qualification data including stability data may be required.

Response: Attached along with this response is a response to the labeling deficiency. Amide has changed the packaging configuration for the 30 count to utilizing a Child Resistant Closure. The new proposed cap is similar to the original metal cap except the new cap is a metal Child Resistant Closure with same inner seal and liner.

In addition to the above amendment Amide is amending its application as follows:

Consumer Products Testing and Laboratory were both contract laboratories proposed in our ANDA application for this product. Both the laboratories were to be utilized interchangeably. In response to changes in other Applications, we are withdrawing Consumer Product Testing Laboratories for the testing of Raw materials from our ANDA application.

All tests will be performed only by Laboratory. CGMP Certification from laboratory was submitted in our original application.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

March 15, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AF

LABELING AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the deficiency letter dated February 17, 1999 enclosed find response to the labeling deficiency as follows:

The closure for the package size of 30's is changed to a child resistant closure.

The initial proposed closure was a metal cap with a Amide is revising the closure to a metal CRC cap with a liner.

The metal cap composition, liner and inner seal for the two closures are same however, the new closure is a metal child resistant closure.

FILED
MAR 17 1999
GENERIC DRUGS

Similarities and differences between the current and proposed closure are listed as follows:

Similarities/ Differences	Current Closure	New Proposed Closure
D		
M D		
C		
		thickness.

Following documents are included to support the changes:

The DMF letter and specifications for the new closure is attached (Attachment I).

Revised specification for the testing of the new closure (Attachment II)

Revised packaging batch record for the package size of 30 tablets using the new closure (Attachment III).

Stability summary for the testing performed to this date for the current container closure system (Attachment IV). This stability data can be applied to the new closure to justify stability dating.

Amide commits to perform accelerated stability studies for the first batch manufactured after approval and will provide the data as soon as it becomes available.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

AC

February 4, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

ADDITIONAL INFORMATION

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to my telephone conversation with Mr. Timothy Ames, enclosed find additional information for our pending ANDA.

Naltrexone Tablets are now an official monograph product in the USP. Amide has revised the analytical method for the active raw material, Naltrexone and for Finished Product Naltrexone Tablets to comply with the USP. Enclosed find a copy of the analytical method and specification for Naltrexone, USP (Attachment I) and for Finished Product Analysis (Attachment II).

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

November 24, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

ORIG AMENDMENT
N/AF

LABELING AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the deficiency letter dated September 24, 1998 enclosed find final printed label and package inserts (12 copies each).

Also included are comparison between the proposed and final printed labels and inserts.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
NOV 25 1998
GENERIC DRUGS

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

August 24, 1998

ORIG AMENDMENT
N/AC

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

MAJOR AMENDMENT

RE: ANDA - 75-274
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the deficiency letter dated June 30, 1998, enclosed find our response.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
AUG 25 1998
GENERIC DRUGS

001

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

April 21, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Room, HFD 630, Room 150
Metropark North II
7500 Standish Place,
Rockville, MD 20855

NDA ONLY AMENDMENT

N/AB

AMENDMENT

RE: **ANDA - 75-274**
NALTREXONE TABLETS

Dear Mr. Sporn:

In reference to the publication of the analytical method for Naltrexone Tablets in the Pharmacopoeial Forum, Volume #24, page # 5911, Amide is amending its ANDA as follows:

The analytical method for dissolution is revised as per the Pharmacopoeial Forum and the bioequivalency deficiency. Enclosed find a copy of the analytical method and specifications (Attachment I).

In reference to the assay method, Amide has performed a comparative study between our in-house assay method versus the proposed method as per Pharmacopoeial Forum. Enclosed find a copy of the comparative study (Attachment II). Based on the results of this study, Amide's in-house method will be used for all testing. We do agree that in case when there is a doubt, the official method will be used. PF methods not official!

Also, enclosed is a copy of the revised Process Validation Commitment certificate (Attachment III). Please replace this certificate from the original application on page 1353)

If you or your staff have any question, please feel free to contact us.

Very truly yours,
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

RECEIVED
APR 22 1998
GENERIC DRUGS

Enc.

ANDA 75-274

Amide Pharmaceutical, Inc.,
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

JAN 12 1998

Dear Sir:

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

NAME OF DRUG: Naltrexone Hydrochloride Tablets, 50 mg

DATE OF APPLICATION: December 15, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 16, 1997

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

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

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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