CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74918

Trade Name Naltrexone Hydrochloride Tablets 50mg

Generic Name Naltrexone Hydrochloride Tablets 50mg

Sponsor Barr Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74918

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74918

APPROVAL LETTER

ANDA 74-918

MAY 8 1998

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated June 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naltrexone Hydrochloride Tablets, 50 mg.

Reference is also made to your amendments dated September 30, 1996, October 21, 1996, May 22, 1997, October 13, 1997 and January 20, and February 26, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Naltrexone Hydrochloride Tablets, 50 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Revia™ (Naltrexone Hydrochloride 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. 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74918

FINAL PRINTED LABELING

Mar 97

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-97
1120902020101

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets
50 mg

Caution: Federal law prohibits dispensing without prescription.

100 Tablets

NDC 0555-0902-02

3 0555-0902-02 7

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

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Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-97
1120902100101

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets

50 mg

Caution: Federal law prohibits dispensing without prescription.

50 Tablets

NDC 0555-0902-10

3 0555-0902-10 2

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-97
1120902100101

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets

50 mg

Caution: Federal law prohibits dispensing without prescription.

50 Tablets

NDC 0555-0902-10

3 0555-0902-10 2

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-97
1120902100101

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets

50 mg

Caution: Federal law prohibits dispensing without prescription.

50 Tablets

NDC 0555-0902-10

3 0555-0902-10 2

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R1-97
1120902100101

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets

50 mg

Caution: Federal law prohibits dispensing without prescription.

50 Tablets

NDC 0555-0902-10

3 0555-0902-10 2

Exp. Date:

Lot No.:

Usual Dosage:
See package brochure.

Dispense with a child-resistant closure in a tight container as defined in the USP.

Protect from light.

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

BARR LABORATORIES, INC.
Pomona, NY 10970

R9-97
1120902010102

BARR LABORATORIES, INC.

Naltrexone Hydrochloride Tablets
50 mg

Caution: Federal law prohibits dispensing without prescription.
30 Tablets
Unit-of-use

NDC 0555-0902-01

3 0555-0902-01 0

Exp. Date:

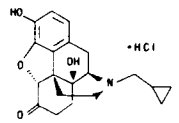
Lot No.:

NALTREXONE HYDROCHLORIDE TABLETS

Revised JANUARY 1998
1009020103

DESCRIPTION:

Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone hydrochloride 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. The chemical name for naltrexone hydrochloride is Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, hydrochloride, (5α)-. The structural formula is as follows:



$C_{20}H_{23}NO_4$ • HCl Molecular Weight: 377.87

Naltrexone hydrochloride is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/cc. Each tablet, for oral administration, contains 50 mg of naltrexone hydrochloride. In addition, each tablet contains the following inactive ingredients: Colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

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 opioid 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-ß-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-ß-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-ß-naltrexol are dose proportional in terms of AUC and C_{max} over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

Absorption:

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-ß-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

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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-ß-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-ß-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-ß-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-ß-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.

Clinical Trials:

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

In one of these studies, 104 alcohol-dependent patients were randomized to receive either naltrexone hydrochloride 50 mg once daily or placebo. In this study naltrexone proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone were shown to have lower relapse rates (21 % vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of naltrexone as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. The 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 Narcotic Addiction: Naltrexone has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

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

The drug is reported to be of greatest use in good prognosis narcotic 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 JUDGMENT OF THE PRESCRIBING PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7 TO 10 DAYS. IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST.

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

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

Treatment of Narcotic 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 addiction.

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. It is not known if this [illegible]

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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. It is not known if there is any cross-sensitivity with naloxone or the phenanthrene containing opioids.
6. Any individual with acute hepatitis or liver failure.

WARNINGS:

Hepatotoxicity:

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

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

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

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

Evidence of the hepatotoxic potential of naltrexone is derived primarily from a placebo controlled study in which naltrexone hydrochloride was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In that study, 5 of 26 naltrexone recipients developed elevations of serum transaminases (i.e., peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone is a direct (i.e., not idiosyncratic) hepatotoxin.

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

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

Unintended Precipitation of Abstinence:

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

While naltrexone is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by naltrexone is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade.

As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Also, lesser amounts of exogenous opioids may prove dangerous if they are taken in a manner (i.e., relatively long after the last dose of naltrexone) and in an amount so that they persist in the body longer than effective concentrations of naltrexone and its metabolites. Patients should be told of the serious consequences of trying to overcome the opiate blockade. (see **PRECAUTIONS: Information for Patients**).

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.

(Over)

When Withdrawal is Accidentally Precipitated 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.

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, you will not perceive any effect. Most important, however, if you attempt to self-administer large doses of heroin or any other narcotic, you may die or sustain serious injury, including coma.

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

Laboratory Tests:

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

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

Drug Interactions:

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

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

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Carcinogenesis:

In a two-year carcinogenicity study in rats, there were small increases in the numbers of mesotheliomas in males, and tumors of vascular origin in both sexes. The number of tumors were within the range seen in historical control groups, except for the vascular tumors in females, where the 4% incidence exceeded the historical maximum of 2%.

Mutagenesis:

A total of twenty-two distinct tests were performed using bacterial, mammalian, and tissue culture systems. All tests were negative except for weakly positive findings in the Drosophila recessive lethal assay and non-specific DNA repair tests with E.coli. The significance of these findings is undetermined.

Impairment of Fertility:

Naltrexone hydrochloride (100 mg/kg, approximately 140 times the human therapeutic dose) caused a significant increase in pseudo-pregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. The relevance of these observations to human fertility is not known.

Pregnancy: Category C.

Naltrexone has been shown to have an embryocidal effect in the rat and rabbit when given in doses approximately 140 times the human therapeutic dose. This effect was demonstrated in rats dosed with naltrexone (100 mg/kg) prior to and throughout gestation, and rabbits treated with 60 mg/kg of naltrexone hydrochloride during the period of organogenesis.

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.

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 subjects 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 hydrochloride can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially narcotic 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: Clinical Trials, *Individualization of Dosage***).

Alcoholism:

In an open label safety study with approximately 570 individuals with alcoholism receiving nal-

[illegible] 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 hydrochloride can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

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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 (5 to 7%), suicidal ideation (2%), and attempted suicide (<1%) have been reported in individuals on naltrexone, placebo and in concurrent control groups undergoing treatment for alcoholism. Although no causal relationship with naltrexone is suspected, physicians should be aware that treatment with naltrexone does not reduce the risk of suicide in these patients (see PRECAUTIONS).

Narcotic Addiction:

The following adverse reactions have been reported both at baseline and during the naltrexone clinical trials in narcotic 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, liching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.**

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

Gastrointestinal: **excessive gas, hemorrhoids, diarrhea, ulcer.**

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

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

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

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

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

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

Other: **depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone used in the treatment of narcotic dependence. No causal relationship has been demonstrated.**

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

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

DRUG ABUSE AND DEPENDENCE:

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

OVERDOSAGE:

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

In the mouse, rat and guinea pig, the oral LD50s were 1,100 +/- 96 mg/kg; 1,450 +/- 265 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 overdose, patients should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date information.

DOSAGE AND ADMINISTRATION:

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

Treatment of Alcoholism:

A dose of 50 mg once daily is recommended for most patients (see CLINICAL PHARMACOLOGY, Clinical Trials, *Individualization of Dosage*).

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 Narcotic 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 narcotic addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.**
2. **If there is any question of occult opioid dependence, perform a naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with naltrexone should not be attempted. The naloxone challenge can be repeated in 24 hours.**
3. **Treatment should be initiated carefully, with an initial dose of 25 mg of naltrexone hydrochloride. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.**

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

Intravenous Challenge: Following appropriate screening of the patient, 0.8 mg of naloxone hydrochloride should be drawn into a sterile syringe. If the intravenous route of administration is selected, 0.2 mg of naloxone hydrochloride should be injected, and while the needle is still in the patient's vein the patient should be observed for 30 seconds for evidence of withdrawal signs or symptoms. If there is no evidence of withdrawal, the remaining 0.6 mg of naloxone hydrochloride should be injected, and the patient observed for an additional [illegible] for signs and

best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

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

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

Intravenous Challenge: Following appropriate screening of the patient, 0.8 mg of naloxone hydrochloride should be drawn into a sterile syringe. If the intravenous route of administration is selected, 0.2 mg of naloxone hydrochloride should be injected, and while the needle is still in the patient's vein, the patient should be observed for 30 seconds for evidence of withdrawal signs or symptoms. If there is no evidence of withdrawal, the remaining 0.6 mg of naloxone hydrochloride should be injected, and the patient observed for an additional period of 20 minutes for signs and symptoms of withdrawal.

Subcutaneous Challenge: If the subcutaneous route is selected, 0.8 mg should be administered subcutaneously, and the patient observed for signs and symptoms of withdrawal for 20 minutes.

Conditions and technique for observation of patient: During the appropriate period of observation, the patient's vital signs should be monitored and the patient should be monitored for signs of withdrawal. It is also important to question the patient carefully. The signs and symptoms of opioid withdrawal include, but are not limited to, the following:

WITHDRAWAL SIGNS: stuffiness or running nose, tearing, yawning, sweating, tremor, vomiting or piloerection.

WITHDRAWAL SYMPTOMS: feeling of temperature change, joint or bone and muscle pain, abdominal cramps, skin crawling, etc.

Interpretation of the Challenge: Warning: the elicitation of the enumerated signs or symptoms indicates a potential risk for the subject, and naltrexone should not be administered. If no signs or symptoms of withdrawal are observed, elicited, or reported, NALTREXONE MAY BE ADMINISTERED. If there is any doubt in the observer's mind that the patient is not in an opioid-free state, or is in continuing withdrawal, naltrexone should be withheld for 24 hours and the challenge repeated.

Alternative Dosing Schedules:

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

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

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

HOW SUPPLIED:

Naltrexone Hydrochloride Tablets are available as follows:

50 mg: Beige, round, biconvex, film-coated, scored tablet. Debossed with b on one side and 50/902 on the scored side.

30	NDC 0555-0902-01
50	NDC 0555-0902-10
100	NDC 0555-0902-02

Dispense in a tight container as defined in the USP.

Protect from light.

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

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

[redacted]

8R-902
Revised JANUARY 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74918

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-918

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road, P.O. Box 2900
Pomona, NY 10970-0519

4. LEGAL BASIS FOR SUBMISSION
The basis for Naltrexone HCl Tablets, 50 mg is REVIA, a prescription drug indicated in the treatment of alcohol dependence and the blockade of the effects of exogenously administered opioids. NDA 18-932 REVIA was approved on November 20, 1984 and is owned by Du Pont Pharmaceuticals.

Patent certification:
There are no patents that claim the listed drug referred to in this application [505 (j) (2)(A)(vii)].

Exclusivity Statement:
According to information published in the list (Cumulative Supplement 12 of the 14th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations), the reference listed drug is not entitled to a period of marketing exclusivity under Section 505 (J)(4)(D) of the Act (or any such periods have expired).

The exclusivity is true for Supplement 12, 1994 14th edition but according to information published in the list of Cumulative Supplement 8 of the 15th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations, the exclusivity for the treatment of alcohol dependence expires on December 30, 1997. The firm is not seeking approval for this indication. Satisfactory.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Naltrexone Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
June 27, 1996: Original submission
May 22, 1997: Amendment
July 14, 1997: amendment correspondence
October 13, 1997: Amendment
January 20, 1998: Facsimile amendment
February 26, 1998: Telephone amendment

FDA:
August 9, 1996: Acknowledgment letter
January 8, 1997: Deficiency letter
December 31, 1997: Facsimile deficiency
February 24, 1998: Telephone call

10. PHARMACOLOGICAL CATEGORY
Opioid receptor antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Film Coated Oral tablet

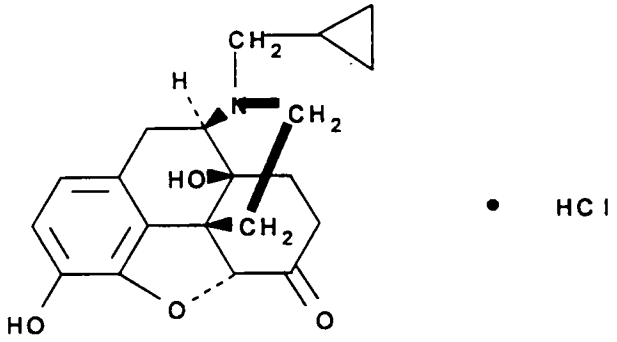
14. POTENCY
50 mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name: 17-(Cyclopropylmethyl)-4,5-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride.

Chemical Formula	Molecular weight	CAS Number
$C_{20}H_{23}NO_4 \cdot HCl$	MW= 377.87	16676-29-2

STRUCTURAL FORMULA:

Naltrexone Hydrochloride



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

16. RECORDS AND REPORTS
Debarment certifications are provided on pages 01-0006/0014.

17. COMMENTS
The following deficiencies are found:

- labeling deficiencies
- EER Pending

18. CONCLUSIONS AND RECOMMENDATIONS
The application can be approved. Approvable letter is pending for labeling and acceptable EER.

19. REVIEWER: S.Basaran, Ph.D.
DATE COMPLETED: 1-26-98/3-5-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74918

BIOEQUIVALENCE REVIEW(S)

ANDA 74-918

NOV 12 1996

Barr Laboratories, Inc.
Attention: Claire M. Lathers, Ph.D.
2 Quaker Road
P.O. BOX 2900
Pomona NY 10970

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Naltrexone Hydrochloride Tablets 50 mg.

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

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

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   > Not less thar Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 6 1996

2.1

Naltrexone Hydrochloride
50 mg Tablet
ANDA #74-918
Reviewer: Moheb H. Makary
WP 74918SD.696

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
June 27, 1996
September 30, 1996
October 21, 1996

Review of a Bioequivalence Study and Dissolution Data

Objective:

The firm has submitted a bioequivalence study under fasting conditions on its 50 mg Naltrexone HCl Tablets and dissolution data to compare the test product relative to Revia® (Dupont Merck) 50 mg Tablets for review. The formulation for the drug product Naltrexone HCl 50 mg Tablets was also submitted.

II. Background:

Naltrexone HCl is a pure opioid antagonist. Its duration of action may be dose-related (24 hr after 50 mg; 72 hr after 150 mg). It is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. It has few, if any, intrinsic actions besides its opioid blocking properties. It does not develop tolerance or dependence.

Following oral administration, naltrexone is rapidly and nearly completely absorbed but undergoes first-pass metabolism. Estimates of the fraction metabolized on first-pass range from 40-95%. The major metabolite is 6β-naltrexol and is believed to be a pure opioid antagonist and may contribute to the opioid receptor blockade. Naltrexone and its metabolites are also conjugated and the free and conjugated (about three times the amount free) forms of parent drug and 6β-naltrexol are excreted renally. About 60% of a total dose may be recovered in the urine after 48 hours. After 24 hours, total base recovered in urine is as follows: 20% as naltrexone (90% conjugated); 70% as 6β-naltrexol (30% conjugated); and, 10% other metabolites. Naltrexone and its metabolites may undergo enterohepatic recycling. Plasma level decline of naltrexone is biexponential over 24 hours, followed by a much slower rate of decline ($t_{1/2}$ = 96 hours) after 24 hours, perhaps due to slow release from tissue sequestration sites. Reported elimination half-lives after oral administration for naltrexone range from 1.1-10.3 hours, and 12.7 hours for 6β-naltrexol.

Plasma concentrations of 6β-naltrexol attain levels 1.5-10 to 10-30 times higher than the parent drug. In animal models, 6β-naltrexol has about 1/12 to 1/50 the opioid antagonist activity. However, the longer $t_{1/2}$ and higher concentrations of 6β-naltrexol (which crosses the blood-brain barrier) may contribute to naltrexone's long duration of action and greater potency

compared to naloxone.

The reference product is Revia® 50 mg tablet, previously named Trexan® (Dupont Merck) approved under NDA #18-932 on 11/20/84.

III. Study #P95-365 for Single-Dose, Two-Way Crossover of Naltrexone HCl Tablets, 50 mg, Under Fasting Conditions:

The objective of the study was to compare the bioavailability of Naltrexone HCl 50 mg tablets manufactured by Barr Laboratories, Inc., with that of Dupont product (Revia®), following an oral administration of a single 50 mg dose (1x50 mg tablet) of each product under fasting conditions.

Clinical site:

Analytical site:

Investigators:

Study design:	Single-dose, two-way crossover bioequivalence study, under fasting conditions.
Study dates:	Period I: March 30 - April 2, 1996 Period II: April 14-17, 1996
Analytical dates:	From April 22 through June 3, 1996.
Washout period:	15 days
Subjects:	Forty-two (42) male subjects were accepted for entry into the clinical portion of the study. Forty-one subjects successfully completed both phases of the clinical portion of the study. Subjects were healthy men 18 to 45 years of age. The weight range was not more than ± 10% for height and body frame as per Desirable Weights for Men-1983 Metropolitan Heights and Weight Table. All subjects completed an acceptable medical history, physical examination, an electrocardiogram, screen for HIV 1&2 antibody, hepatitis B surface antigen and drugs of abuse prior to study initiation. Selected routine clinical laboratory measurements were performed during screening.
Exclusion criteria:	Consisted of adverse reactions or allergy to naltrexone or related drugs, history of alcohol or drug abuse, history of cardiovascular, neurological,

neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases.

Instructions: Subjects were instructed not to take any drugs within 7 days of period I dosing. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 48 hours prior to, and during the course of the study.

Dose and treatment: Treatment A; 1x50 mg Naltrexone HCl tablet (Barr), lot #6R90208, batch size tablets, potency 99.9%, content uniformity 100.0% (CV=1.7%), administered following a 8 hours overnight fast.

Treatment B: 1x50 mg Revia® tablet (Dupont), lot #J0398A, EXP. 1/98, potency 101.7%, content uniformity 102.0% (CV=1.2%), administered following a 8 hours overnight fast.

Food and fluid intake: Subjects fasted for eight hours prior to dosing. Lunch was served four hours after dosing. Dinner was served ten hours after dosing. Water was not allowed from 1 hour prior to dose administration until 2 hours after dosing, except for the dosing water (240 mL).

Blood samples: Ten mL (10) blood samples were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing. Plasma samples were immediately frozen.

Subject welfare: Vital signs (blood pressure and heart rate) were measured pre-dose and at 12 and 24 hours after each dose and upon completion of the study.

Assay Methodology:

Statistical Analysis

Statistical analysis was performed on naltrexone and 6β-naltrexol data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two

one-sided tests were used to estimate the 90% confidence interval.

IV. In Vivo Results:

Forty-two (42) normal, healthy subjects were recruited for the study. Forty-one (41) successfully completed both phases of the clinical portion of the study. On study day 7, subject #22 developed fever, sore throat, headache and stuffy nose. The subject reported using medications over the course of the study. Subject #22 was dropped prior to period II dosing by the clinical investigators secondary to medications consumed between study period I and II. Failure to complete the study was not related to study product. Fifty-five adverse events were reported in twenty-four of forty-two subjects dosed and included the following events: anorexia (2-loss of appetite), arthralgia (1-right knee pain), back pain (2), dizziness (5), upset stomach (4), edema flushes (2), nausea (7), pain (2; 1-left arm pain, 1-right arm pain), pallor (1-pale), pharyngitis (3-sore throat), purpura (2), rigors (1-chill), skin cold clammy (2-clammy), sweating increased (1) and vomiting (3). Of the fifty-five reported adverse events, thirty were probably or possibly related to study drug. In the opinion of the investigators, the other twenty-five adverse events were either remotely related to or unrelated to study drug. There were no serious adverse events or any events which required terminating any subject from the study.

The plasma concentrations and pharmacokinetic parameters for naltrexone and 6β-naltrexol are summarized in Tables I and II.

Table I

Mean Plasma Naltrexone Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 50 mg Naltrexone HCl (1x50 mg Tablet) Under Fasting Conditions

(N=41)

Time hr	Treatment A Barr-Test Lot #6R90208 ng/mL (CV)	Treatment B Dupont-Reference Lot #J0398A ng/mL (CV)
0	0	0
0.25	0.21 (291)	0.25 (221)
0.5	3.81 (131)	3.49 (83.3)
0.75	6.17 (82.8)	6.13 (55.8)
1	6.23 (68.4)	5.92 (51.7)
1.33	5.64 (64.2)	5.41 (46.3)
1.67	4.92 (66.4)	4.94 (44.9)
2	4.52 (63.5)	4.66 (46.3)
2.5	3.96 (57.6)	4.49 (59.7)
3	3.40 (59.1)	3.79 (62.7)
4	2.40 (60.8)	2.64 (66.6)
6	1.32 (86.0)	1.47 (76.5)
8	0.57 (132)	0.67 (106)
10	0.29 (158)	0.28 (179)
12	0.18 (216)	0.16 (207)
16	0.03 (460)	0.03 (447)
24	0	0
36	0	0
48	0	0
72	0	0

			90% CI
AUCTLQC (ng.hr/mL)	22.05 (75.5)	23.29 (59.7)	
AUCinf (ng.hr/mL)	24.31 (69.9)	25.30 (55.9)	
Cmax (ng/mL)	7.21 (69.3)	7.19 (47.1)	
Tmax (hr)	1.13	1.12	
Kel (1/hr)	0.32	0.31	
T1/2 (hr)	2.37	2.45	
LnAUCTLQC			84-101%
LnAUCinf			87-102%
LnCmax			84-106%

1. For naltrexone, the least squares means for AUCTLQC, AUCinf and Cmax values were 5.4%, 4.1% and 0.1% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence

intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The naltrexone plasma levels peaked at 0.75 and 1 hour for the reference and the test products, respectively, following their administration under fasting conditions.

3. Subjects #2 (period II), 10 (period II) AND 12 (period I) experienced vomiting episodes at 2.7, 3.5 and 3 hours, respectively, after dosing. Since all vomiting events occurred at least 2.5 hours after drug administration, these episodes should not affect the outcome of the study.

Table II

Mean Plasma 6β-Naltrexol Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 50 mg Naltrexone HCl (1x50 mg Tablet) Under Fasting Conditions
(N=41)

Time hr	Treatment A Barr-Test Lot #6R90208 ng/mL (CV)	Treatment B Dupont-Reference Lot #J0398A ng/mL (CV)
0	0	0
0.25	3.73 (153)	4.59 (132)
0.5	41.84 (63.9)	40.38 (68.3)
0.75	65.61 (38.9)	64.08 (41.5)
1	66.59 (31.1)	63.67 (38.0)
1.33	60.65 (30.0)	59.07 (32.7)
1.67	54.76 (29.0)	57.15 (32.4)
2	52.62 (30.8)	54.10 (26.0)
2.5	50.52 (22.4)	53.61 (25.3)
3	47.25 (23.0)	48.76 (25.4)
4	39.03 (22.6)	39.84 (23.7)
6	31.45 (24.1)	32.44 (28.4)
8	24.95 (25.9)	25.16 (28.9)
10	19.95 (28.4)	20.77 (28.9)
12	17.49 (27.9)	17.77 (27.0)
16	12.97 (27.0)	13.58 (26.5)
24	8.95 (26.3)	8.99 (25.1)
36	4.22 (38.1)	4.49 (34.6)
48	2.37 (37.1)	2.33 (37.6)
72	0.58 (95.7)	0.66 (81.5)

			90% CI
AUCTLQC (ng.hr/mL)	692.43 (22.3)	710.03 (22.9)	
AUCinf (ng.hr/mL)	715.70 (22.0)	731.10 (22.5)	
Cmax (ng/mL)	77.20 (25.6)	76.01 (28.5)	
Tmax (hr)	1.18	1.45	
Kel (1/hr)	0.055	0.055	
T1/2 (hr)	12.99	12.98	
LnAUCTLQC			94-102%
LnAUCinf			94-102%
LnCmax			94-110%

1. For 6β-naltrexol, the least squares means for AUCTLQC, AUCinf and Cmax values were 2.5%, 2.2% and 1.3% lower and higher respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The 6β-naltrexol plasma levels peaked at 0.75 and 1 hour for the reference and the test products, respectively, following their administration under fasting conditions.

3. Plasma concentrations for 6β-naltrexol attained approximately 10 times higher levels than the parent drug.

V. Formulation:

Barr's formulation for its Naltrexone HCl 50 mg Tablets is shown in Table III.

VI. In Vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of water
Number of Tablets:	12
Test product:	Barr's Naltrexone HCl tablets, 50 mg, lot #6R90208
Reference product:	Dupont's Revia® tablets, 50 mg, lot #J0398A
Specification:	NLT in 60 minutes

Dissolution testing results are shown in Table VI.

VII. Comments:

1. The firm's single-dose bioequivalence study #P95-365 under fasting conditions, conducted on its 50 mg Naltrexone HCl tablet is acceptable. The 90% confidence intervals for LnAUCTLQC, LnAUCinf and Cmax are within the acceptable range of 80-125% for Naltrexone and 6β-naltrexol.

2. The in vitro dissolution testing for the test product 50 mg Naltrexone HCl tablets is acceptable.

VIII. Recommendations:

1. The single-dose bioequivalence study #P95-365, conducted by Barr Laboratories Inc., on its Naltrexone HCl 50 mg Tablets, lot #6R90208, comparing it to Revia® 50 mg Tablets manufactured by Dupont Merck, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Barr's Naltrexone HCl 50 mg Tablets is bioequivalent to Dupont's Revia® 50 mg Tablets.

2. The dissolution testing conducting by Barr Laboratories Inc., on its Naltrexone HCl 50 mg Tablets, lot #6R90208 is acceptable. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

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

The firm should be informed of the above recommendations.

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 11/1/96

Concur: Date: 11/6/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/10-31-96 wp 74918SD.696
cc: ANDA #74-918, original, HFD-658 (Makary), Drug File, Division File.

Table VI

Results of In Vitro Dissolution Testing						
Sampling Times Minutes	Test Product Lot #6R90208 Strength 50 mg			Reference Product Lot #J0398A Strength 50 mg		
	Mean%	Range	%CV	Mean%	Range	%CV
15	40		10	54		6
30	80		4	87		3
45	96		2	99		2
60	98		2	101		2

Table III

Following is a full statement of the composition of the dosage formulation:

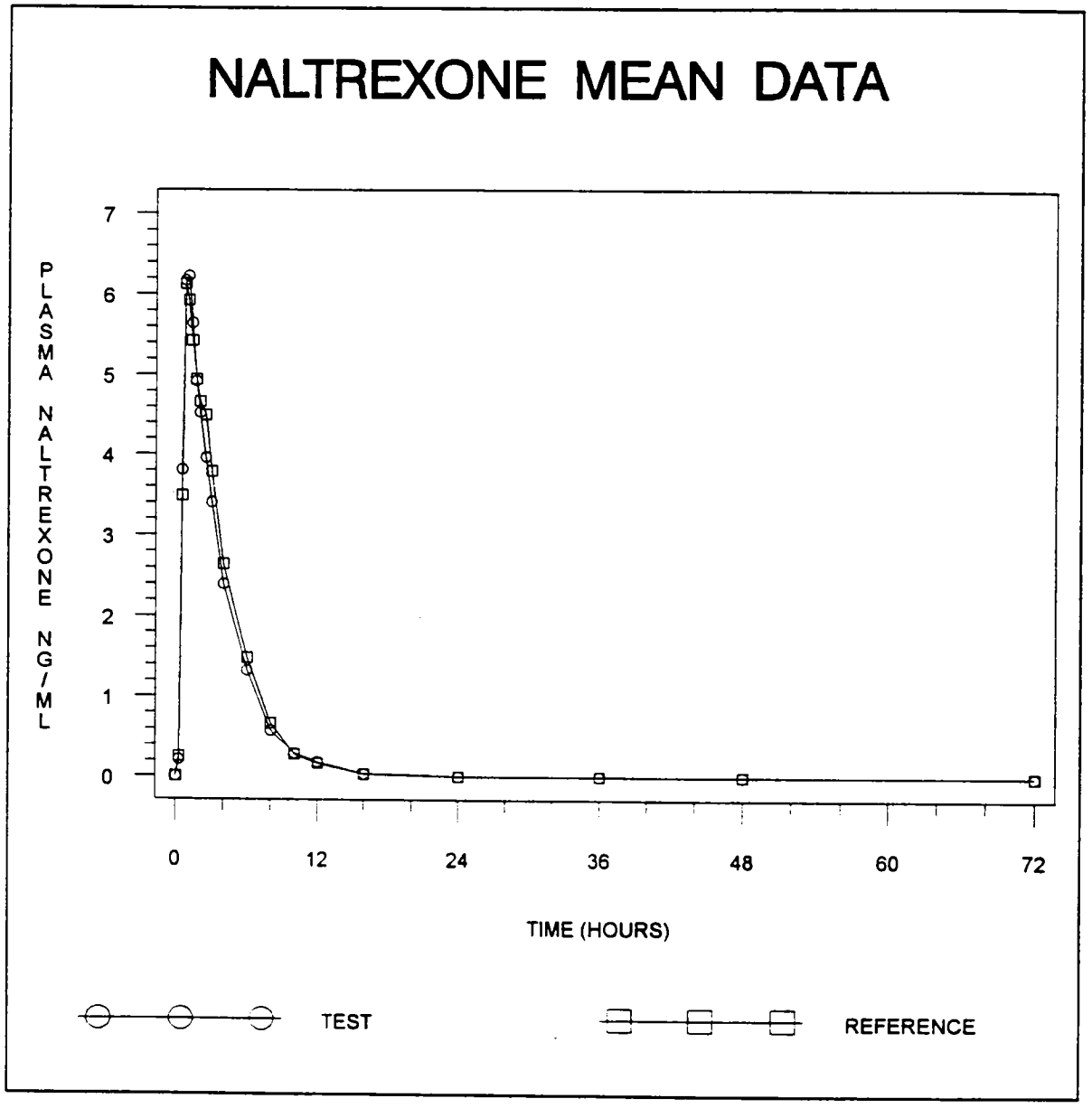
Naltrexone Hydrochloride Tablets, 50 mg

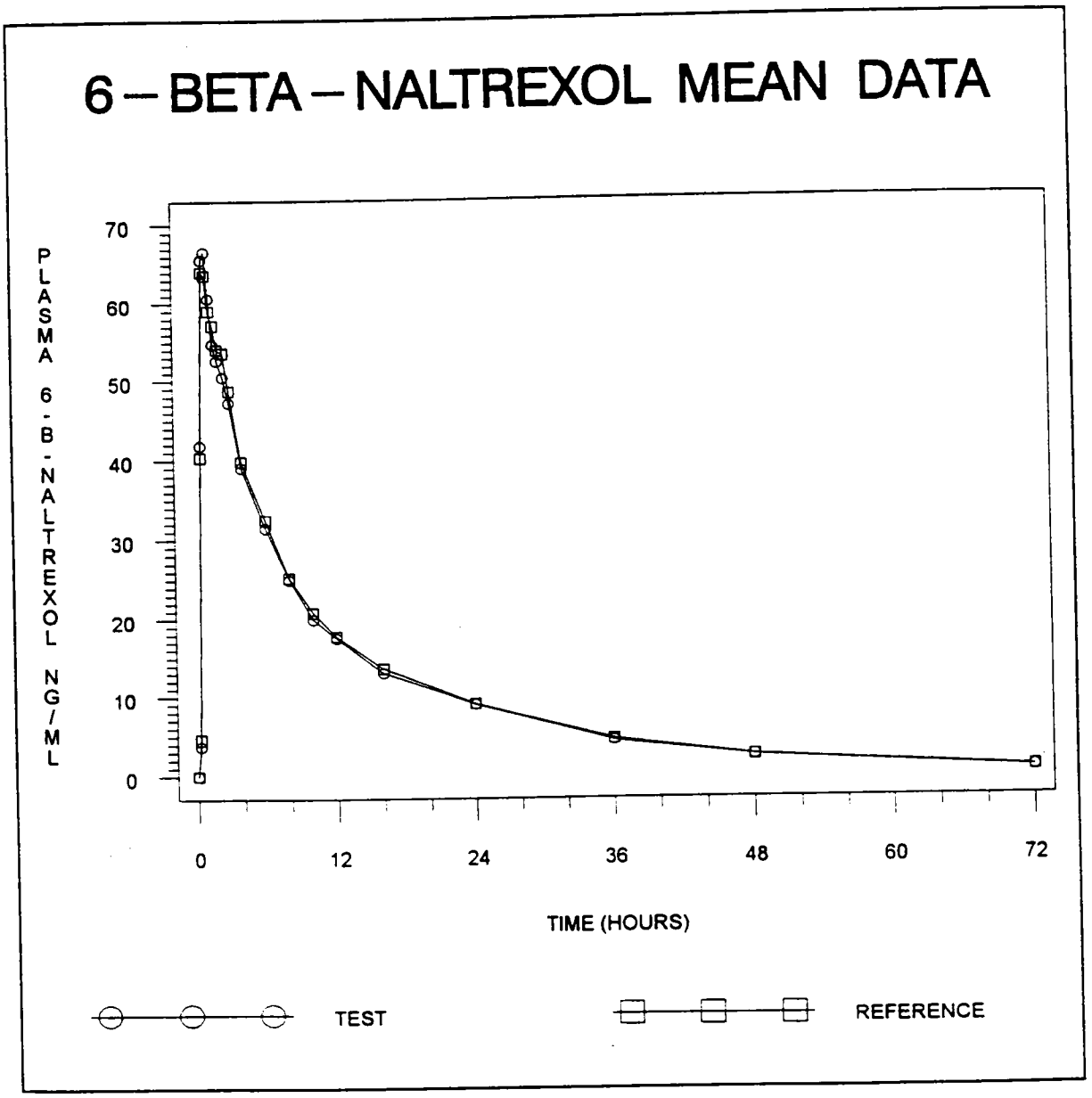
Ingredients	mg/Dose
Naltrexone Hydrochloride	50.00*
Lactose Monohydrate, NF	
Lactose Monohydrate, NF	
Colloidal Silicon Dioxide, NF	
Magnesium Stearate, NF	
Crospovidone, NF	
Microcrystalline Cellulose, NF	
Colloidal Silicon Dioxide, NF	
Magnesium Stearate, NF	
Core Tablet Weight	300.00 mg

Film Coating Dispersion

Beige
Purified Water, USP

* Weight adjusted according to the assay value (as is basis).
** To be adjusted for total weight.


NALTREXONE MEAN DATA
PLASMA NALTREXONE NG/ML
0
1
2
3
4
5
6
7
0
12
24
36
48
60
72
TIME (HOURS)
TEST
REFERENCE


6 – BETA – NALTREXOL MEAN DATA
PLASMA 6-B-NALTREXOL NG/ML
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
TIME (HOURS)
TEST
REFERENCE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74918

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-918

DRUG PRODUCT: Naltrexone Hydrochloride Tablets, 50 mg.

FIRM:Barr Laboratories, Inc. DOSAGE FORM: Tablet

STRENGTH: 50 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Vol. 1.1. on page 09-00025).
EIR update : Requested on 11-21-96. Acceptable on 10-6-97. Update requested. Pending.

BIO STUDY: Satisfactory.
Biostudy was reviewed by M. Makary and found acceptable on 11-6-96.

Bio. dissolution specification same as manufacturing:
NLT (Q) in 60 minutes.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Acceptable by NE Lab(HFR-NE560) on Naltrexone HCl Tablets and drug substance. See HFR-NE560 memorandum on May 29, 1997. Vol.2.1.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

Summary of container/closure system:
For 30, 50 and 100 count:
Bottles: 75 cc round, white, HDPE
Resin:
Colorant:
Manufacturer:

Cap: 33-400 white plastic
Outer cap resin:

Inner-cap:
Lining material:

Colorant:
Manufacturer of closure:
Filler:
Manufacturer:

LABELING:
Satisfactory per A.Vezza on 1-?-98.

STERILIZATION VALIDATION (IF APPLICABLE):
NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Naltrexone HCl tablets , 50 mg batch # 6R90208 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Barr's Naltrexone HCl 50 mg Tablets is bioequivalent to Dupont's via 50 mg Tablets.

The size of the bio batch was tablets(lot #6R90208).
Firm's source of NDS OK : Yes

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
For 50 mg tablets: Executed batch size: ablets,Lot # 6R90208

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
For 50 mg tablets: ablets.

Manufacturing process is the same as bio.stability.

CHEMIST: S. Basaran DATE:1-26-1998 S. Basaran 1/30/

Team Leader: U. Venkataram DATE: 1-28-1998 U.V. Venkataram 2/1/98