# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 75-434

# **APPROVED DRAFT LABELING**

## FINAL PRINTED LABELS

NDC 0185-0039-30 Each tablet contains: Naitrexone USUAL DOSAGE: See ĕ Naltrexone HCI.....50 mg accompanying literature for complete prescribing in-No.: Hydrochloride 0185-0039-3 KEEP TIGHTLY CLOSED. **Tablets** Store at controlled room tem-KEEP THIS AND ALL MED-ICATION OUT OF THE REACH DE CHILDRED perature 15°-30°C (59°-86°F). Protect from light. 50 mg Dispense in tight, light-resistant containers as defined in the USP, with a child-Rx only 30 Tablets resistant closure, as required. MAR -8 2000 Issued 2/98 Eon Labs

NDC 0185-0039-01 Each tablet contains: DOSAGE: See **Naltrexone** USUAL Lot No.: Naltrexone HCI.....50 mg accompanying literature for Hydrochloride 0-6 complete prescribing in-KEEP TIGHTLY CLOSED. **Tablets** Store at controlled room tem-KEEP THIS AND ALL MEDperature 15°-30°C (59°-86°F). THE REACH 50 mg Protect from light. 85-( This is a bulk package. Dispense in tight, light-resistant containers as defined Rx only 5 100 Tablets in the USP, with a child-MAR -8 2000 resistant closure, as required. Eon Labs Issued 2/98

## NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

Rx only

DESCRIPTION:
Natizzone hydrochloride, an opioid amagonist, is a synthetic congener of drymorphone with no opioid agonist properties.
Natizzone differs in structure from drymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylimethyl group. Natizeone hydrochloride is also related to the potent opioid antagonist, natione, or n-atylinoroxymorphone, and is designated as: 17-(Oyclopropylimethyl)-4,50-epoxy-3,14-diaydroxy-morphinan-6-one hydrochloride. The structural formula for natizeone hydrochloride is shown below:



CaniforNO4HCI

Natiresone hydrochloride is a white, coetalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. Each tablet 100 mg/mL is called the salt of the saltent of about 100 mg/mL is called the saltent of the saltent

### CLINICAL PHARMACOLOGY:

Pharmacolymanic Actions:
Nattreame is a pure opioid antiquosis. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids.
When co-administered with morphine, on a chronic basis, nattrexone blocks the physical dependence to morphine, teroin and other opioids.
Nattreaments are set as, if any, intrinsic actions besides its opioid blocking properties. However, if does produce some pupillary constition, by an unknown mechanism.
The administration of nattreame hydrochloride is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, natureone well precipitate withdrawal symptomatology.
Clinical studies indicate that 50 mg of natirezone hydrochloride will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Offer data suggest that doubling the does of natirezone provides blockade for 48 hours, and tripling the dose of natirezone provides blockade for 48 hours, and tripling the dose of natirezone provides blockade for about 72 hours.
Natirezone blocks the effects of opioids by competitive binding (i.e., nakoposis to competitive shibition of entymens) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full natireone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

by administration of very ingin obles or opases has resumed in excessive symptoms or instantian reveals in experimental subjects.

The mechanism of action of nathresone in alcoholism is not understood; however, involvement of the endogenous opioids system is suggested by preclinical data. Nathresone, 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 nathresone has been shown to reduce alcohol consumption in chinical studies.

Nathresone is not aversive threspy and does not cause a disulfiram-like searchin either as a result of opiate use or

ethanol injection.

Natrezone is a pure opioid receptor antagonist. Although well absorbed orally, nattrezone is subject to significant first.

Natrezone is a pure opioid receptor antagonist. Although well absorbed orally, nattrezone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%. The activity of nattrezone is believed to be due to both parent and the 6-6-natrezol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 75% of the dose), however, univary excretion of unchanged matterone accounts for less than 2% of an ord dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (1-1/2) values for nattresone and 6-6-natrezol are dose proportional in terms of AUC and C<sub>max</sub> over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

According to the service of the companies of the extensional matter of the service of the servic

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

Metabolism:
The systemic clearance (after intravenous administration) of naltrexone is -3.5 Umin, which exceeds liver blood flow (-1.2 Umin). This suggests both that naltrexone is a highly extracted drug (-98% metabolized) and that extra-heptic sates of drug metabolism usies. The major metabolist of nativoren is 6-β-nativezol who other minor metabolist are 2-hydroxy-3-methoyy-6-β-nativezol and 2-hydroxy-3-methoyy-nativexone, and its metabolistes are also conjugated to form additional metabolis products.

also conjugated to form deficient metabolic products.

Elimination:

The deficient of the d

The pharmacokinetic profile of nathrocone suggests that nathresone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impaltment:

Matteroom appears to have extin-chepatic actes of drug metabolism and its major metabolite undergoes active tubular secretion (see Metabolism above). Adequate studies of nathresone in patients with severe hippatic or renal impatiment secretion (see Metabolism above). Adequate studies of nathresone in patients with severe hippatic or renal impatiment secretion (see Metabolisms and above). Adequate studies of nathresone in patients with severe hippatic or renal impatiment of the secretion (see Precal ITONS). Special Risk Patients).

Clinical ITaits.

Attacholisms.

The efficacy of nathresone as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double billoid trials. Thest studies used a dose of nathresone hydrochloride tablets, 50 mg once daily or 12 weeks as an adjunct to social and psychotharapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, demential, and secondary psychotiatic disgnoses were excluded from these studies. In one of these studies, 104 sicohol-dependent patients, the group of patients study, nathresone proved superior to placebo in measures of dinking including abstraction rates (51% vs. 25%), number of dinking days, and religies (31% vs. 50%). In a second study with 82 alcohol-dependent patients, the group of patients receiving nathresone were shown to have lower subpase rates (12% vs. 45%), less allowed craving, and fever dinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of nathresone as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter subty study. This shouly of 855 individuals with alcoholism included patients with comorbid psychiatic conditions, concomitant medications, polyquotance abuse and HIV disease. Results of this study

conditions, concombant medications, polysubstance abuse and NIV disease. Results of this study genonstrates that he side effect profile of nathersome appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon. In the clinical studies, Internate with nathratone supported abatinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abatinence and relapse were similar to those observed in the controlled studies. Natireation was not uniformly height to all patients, and the expected effect of the drug is a modest improvement in the octoome of conventional treatment. Treatment of opioid Additions. Natireations are supported to 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 occaine or other non-opioid drugs of abuse. There are no data that demonstrate an unequivocably beneficial effect of nativezone on rates of recidinism among detecting, 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 control, or other compliance-enhancing protocol. Natirezone, unlike methadone or LAMM (levo-alpha-acty)methadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under extensic conditions that support continued use of the medication. Individual area of the compliance-enhancing protocol. Natirezone, unlike the enhanced of Atendrolism:

PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7-10 DAYS. IF THERE IS ANY OURSTION OF COULT OPIOID OF PENDENCE, PERFORM A NALOXONE CHALLENGE TEST.

Treatment of Atendrolism:

ANY OUESTION OF OCCULI OWNIU DEPTAUENCE, PERFORM IN ABSOLUTE OF SEASON IN CONTROLLED AND ANY OF SEASON IN CONTROLLED AND ANY OF SEASON IN CONTROLLED AND ANY OF SEASON IN CONTROLLED ANY OF SEASON IN

effective than any other in reducing these complaints for all patients.

Trastment of Opicid Departments:

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

measure to ensure the patient takes the medication.

A flexible approach to a doginal regimen may be employed to enhance compliance. Thus, patients may receive 50 mg of natientom light duplication and the series of the control of t

INDICATIONS AND USAGE:

natirezione is indicated: In the treatment of alcohol dependence and for the blockade of the effects of poenously administered opioids. Natirezione has not been shown to provide any therapeutic benefit except and appropriate plan of management for the addictions.

Nattreone has not been shown to provide any therapeutic benefit except an appropriate plan of management for the addictions.

CONTRAINDICATIONS.

CONTRAINDICATIONS.

1) Patients contraindicated in:

1) Patients receiving opioid analogesics.

2) Patients currently dependent on opioides.

3) Patients in acute opioid vehibulawal (see WANINICS).

4) Any individual with a history of sensitivity to natirezone or any other components of this product. It is not known if there is any tons-reservibly with halaxons or the phenanthrene containing opioids.

5) Any individual with a cutte hepatitis or liver failure.

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

Mathetone is contraindicated in acute hepatitis of ther fallers, and its use in patients with active tiver disease must be carefully considered in light of its hepatioloxic affects.

The margin of separation between this apparately said does not nativezone and the does cassing hepatic injurappears to be only five-told or less. Maitrazone does not appear to be a hepatoloxin at the recommender.

deses. Palients should be warned of the risk of hepatic injury and advised to stop the use of natirazone and see medical attention if they experience symptoms of acute hepatitis.

medical attention in they apperience symptems of acris hepatitis.

Evidence of the hepaticistic potential of natincone is derived primarily from a placebo controlled study in which natincone hydrochlorids was administered to obsess subjects at a does approximately five-lost that recommended for the blockade of opies receptors (300 mg per day). In that study, 5 of 26 natincone recipients developed devations of serum transaminases (is, peak ALT values ranging from a low of 12 to a high of 552; or 3 to 19 times their baselies 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—one was obtained returned to (or fourard) baseline values in a matter of weeks, the back of any transaminase elevation on whom follow—one was obtained returned to (or fourard) baseline values in a matter of weeks, the back of any transaminase elevation on whom the description of a similar magnitudes in any of the 24 placebo patients in the same study is presuative evidence that natizenous is a direct (i.e. not ideopticatic) hepationian or opies backeds (510 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than did placebo, transaminase elevation in one of the patients of the control of the co

administration of nativazone. The nativazone challenge test is described in the DOSAGE AND ADMINISTRATION excites.

Attempt to Overcome Blockade;
While nativazone is a potent antaponist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by nativazone is summountable. This is useful in parients who may require analysis, but poses a potential risk to individuals who strampt, on their own, to overcome the blockade by administering tamps amounts of exopensos opioids included, any sitempt by a potient to overcome the antaponism by tabing opioids in very damperous and may lead to a fatal overdose, fully may arise because the plasma concentration of exopensos opioids attained immediately following their acuts administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be immediate danger or suffering file endangering opioid infockation (e.g., respiratory arrest, circulatory collapses). Patients schools be told of this serious consequences of trying to overcome the opisite blockade. (See internation for Patients section).

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

ULTRA Rapid Opioid Withdrawst: Sale use all natirezone in rapid opiate detaxification programs has not been established (see ADVERSE REACTIONS).

PRECAUTIONS:

PRECAUTIONS:
General:
When Reversal el Nattrazone Blockade la Regulired: In an emergency situation in patients receiving fully blocking doses of natirezone, a suggested plan of management is regional analysesia, conscious sedición with a benzociarpine, use of non-foolid stratgesco or general anasthesia. In a situation requiring opioid analysesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be despet and more prolonged.
A rapidly acting opioid analysesic which minimizes the duration of respiratory depression is preferred. The amount of analysesic deministered should be titrade to the needs of the patient. Non-receptor mediated actions may occur and should be supercised (e.g., bacial swelling, fiching, generalized srythema, or bronchoconstriction) presumably due to historiame release.
Insepercise of the drug chosen to reverse nattercone blockade, the patient should be monitored closely by appropriately trained personal in a setting equipped and staffed for cardiopulmonary resuscitation.
Academially Practificated Withdrawal: Swerze opioid withdrawal syndromes precipitated by the accidental ingestion of analtezone have been reported is opioid-dependent individuals. Symptoms of websites that we usually appeared within live minutes of engestion of nathronous and have lasted for up to 45 hours. Marrial strust changes including contrations and produces of the contrations have occurred. Significant fluid losses from venning and distrine have required marrial subored to nest individual requirements. Patients were aclosely monitored and therapy with non-opioid medications was tallowed to nest individual requirements of the patients of the patients.

Next the patients.

Naticone and its primary metabolise are secreted primarily in

he drug to patients with renal impairment. He patient with renal recovering the drug to patients with level approximate, the drug to patients with level approximated. An increase in nativesone AUC of approximately 5- and 10-loki in patients with compensated and decompensated liver circlesis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that attentions in nativesone blobanishings are tested to liver disease severity.

Salidiše:

The rak of salicidis is known to be increased in patients with substance abuse with on white additional patients and the patients of the patient

mcleding coma.
Natirezone 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 abdomical pain tasting more than a few days, white bowel
movements, dark urine, or yellowing of your eyes, you should stop taking natirezone immediately and see your doctor

Laboratory Tests:

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

Nattrevone does not interfer with historyet post-inguil, and high pressure injury distributions produced the separation and detection of morphina, methadone or quinnes in the urine. Natirezone 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 Infernations:
Studies to evaluate possible interactions between nathresone and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of nathresone and other drugs is required. The safety and etilizary of concomitant use of natification and disultinam is unknown, and the concomitant use of two potentially heaptoniax medications is not ordinary recommended unless the probable benefits outweigh the known take.

Lethargy and somnolence have been reported following doses of nattresone and thioridazine. Patients taking nathresone may not benefit from opioid containing medicines, such as cough and cold preparations, anticistrate preparations, and opioid nanalesists. In an emergency situation when opioid analgesia must be administered to a patient receiving nathresone, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged (see PRECAUTIONS).

Carcinogensia, Metagenesia 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 metabolist 6-9-nativesol are unknown.

In a two-year carcinopeniony study in rats, there were small increases in the numbers of testicular mesorheliomas in males and tumors of vascular origin in males and temales. The incidence of mesorhelioma in males given natification at a dietary dose of 100 mp/mp/day (500 mp/m²/day). It 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 mp/m²/day (500 mp/m²/day) was 4%, but only the incidence in females was increased compared with a maximum historical central incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with nattreaone in male and female mice.

There was limited evidence of a weak genotoxic effect of natirexone in one gene mutation assay in a mammalian cell fine, in the *Drosphila* recessive lethal assay, and in non-specific DNA repair tests with £. coll. However, no evidence of genotoxic potential was observed in a range of other in vizzo test, lockliding sassays to gene mutation in bacteria, yeast or in a second mammalian cell line, a chromosomal abstration assay, and an assay for DNA damage in human cells. Natzecone did not schild classoperisticy in an in vizzo mouse micronocleus assay.

Pregnancy: Category C. The following statement

Pregnancy: Category C.

The following statements are based on the results of experiments in rats. The potential reproductive toxicity of the metabolite 6-β-trainists in rats is not known.

Natirezone increased the incidence of early fetal loss when administered to rats in oral doses ≥30 mg/kg/day (180 mg/mk/day; Chimss the recommended therapeutic dose, based on body surface area] and to rabbits at oral doses ≥60 mg/kg/day (120 mg/mk/day; 18 limes the recommended therapeutic dose, based on body surface area. There was no evidence of teradopenicity when notificence was administered orally for tax and rabbits autoring the period of major organogenesis at doses up to 200 mg/kg/day (32 and 65 times the recommended therapeutic dose, respectively.

major organogenesis at doses up to 200 mg/kg/day (32 and 65 times the recommended therapeutic dose, respectively, based on body surface acea).

There are no adequate and well-controlled studies in pregnant women. Nattrexons should be used in pregnancy only when the potential benefit justicies the potential risk to the lefus.

Labber and Delivery:

Whither or not anterzone affects the duration of labor and delivery is unknown.

Narrising Mothers:

Whether or not hatterzone is excreted in human milk is unknown. Because many drugs are excreted in human milk, caution should be exercised when nattrexone is administered to a nursing woman.

Petitable Use.

Pressure use:
The safe use of natirezone in pediatric patients younger than 18 years old has not been established.
Post Marketing Experience:
Adverse events, including withdrawed symptoms and death, have been reported with the use of natirezone hydrochlor in uttra rapid opiate defloat/calidation programs. The cause of death in these cases is not known (see WARMINGS).
ADVERSE REACTIONS:

an utra rapid opeas enteriorization programs. The cause of ocean in these cases a not known (see Warkinstos). 
During the randomized, double-billed placebo-controlled 12 week trials to evaluate the efficacy of natirectors as an 
adjunctive trainment of alcohol dependency, most patients tolerated nativerone well. In these studies, a total of 53 
patients received the program of the propriet during these two trials. 
While contained extensive the profited during these two trials. 
While contained colors extending the use of nativerone in determined, point dependent individuals 
take to identify any single, serious unforward risk of nativerone use, placebo controlled studies employing up to (twi-loid 
higher doses of nativerone hydrochoride (up to 30 cm per dry) than that recommended for use in opiate receptor 
blockage have shown that nativerone causes hepatocellusir iniumy in a substantial proportion of patients exposed at 
higher doses is Sew WARNINGS AMP PRECAUTIONS 1. Laberatory Testa.). 
Asade from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate nativesore, 
used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid free," it is critical to 
recompletely free of exogenous opioids.

recognize that natiresone can precipitate or exacethate 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 shorzery 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 ratherone.

Among opioid free individuals, natirezone 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, natirezone may cause serious withdrawal reactions (see CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION).

Reported Adverse Events

National Adverse Events

National Adverse Events

National National Adverse Events

National National Adverse Events

National to be free of opioids for more than 7-10 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 synthemic complex consisting of learn/lines, mid nauses, advantial carpine, resitessness, bone or joint pain, mystips, and nausal symptoms. This may represent the unmasking of occur opioid use, or it may represent symptoms attributable to nautrezone. A number of attential dealing patterns have been recommended to try to reduce the frequency of these complaints (see Individual Existing of Dawage).

Alcoholism: In an open hole safety study with approximately 570 individuals with alcoholism receiving natirezone, the following new-onest adverse reactions occurred in 2% or more of the patients: nausea (10%), headcake (7%), dizziness (4%), nervousees (4%), latique (4%), essemina (3%), ownsing (3%), an unsity (2%) and somnolence (2%). Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing natirezone, placebo or controls undergoing treatment for alcoholism.

RATE RANGES OF NEW ONSET EVENTS

Natirezone Placebo
Depression 0-15% 0-15% 0-17%
Suicide Altempt/Ideation 0-1% 0-3%
Athough no causar relationship with natirezone is suspected, physicians should be aware that treatment with natirezone does not reduce the risk of suicide in these patients (see PRECAUTIONS).
Depinia Addiction:

Update Assistant:
The following adverse reactions have been reported both at baseline and during the natirezone clinical trials in narcotic addiction at an incidence rate of more than 10%.
Difficulty steeping, anxiety, nervousness, abdominal past/cramps, nausea and/or vornising, low energy, joint and muscle pain, and headcabe.

pain, and headache.

The incidence was less than 10% for:
Loss of appartie, distribud, constitution, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, debyed disculation, decreased potency, and chills.

The following events occurred in less than 1% of subjects;
Respiratory, mast congestion, sching, minormes, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breating, hourseness, cough, shortness of breath.

Curriovascular: nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, table-early.

Wusculoskeltzi, painful shoulders, legs or knees: tremors, (witching, Gentournary: necessed frequency of, or discomfort during, unration, necreased or decreased sexual interest. Dematologia: Vols kin, priumus, ance, athletés foot, cold soires, alopecia. Psychiatric: depression, paranoia, latique, resilessness, confusion, disorientation, hallucinations, nightmares, bad

Psychiatric depression, paranoia, latique, restlesaness, conflusion, disorientation, hallucinations, nightmares, bad dreams.
Special senses eyes-blurred, burning, light sensitive, wollen, aching, strained, ears. "clopped", aching, intrinuts, General increased appetite, weight (pain, yawning, sommolence, lever, dry mouth, head "pounding", Post-marketing Esseriences. Data collected from post-marketing use of nativesone show that most events usually occur sally in the course of drug therapy and are transient. It is always possible to distinguish these occurrences from those signs and symptoms. Enter may result from a withdrawal syndrome. Events that have been reported include ancressa, asthenia, cheap pain, fatique, headache, hot flushes, makine, changes in blood pressure, agistion, dizmess, hyperkinesia, nauses, vonning it may result from a withdrawal syndrome. Events that have been reported in control abnormalities or hepatics, patriations, mysligia, susiety, conclusion, euphoria, hallucinations, insomnia, nervousness, ommolence, abnormal filmismic, olysprear, rash, increased sweating, and vision abnormalities. Or spread in the patrial control of the control of the control of the control of the patrial restrainship has been demonstrated. In the leterature, endogenous coincids have been theorized to contribute to a variety of conditions. In some individuals the use of opioid antiagonists has been associated with a change is in not fully understood.
Adverse evers, including withdrawal symptoms and death, have been reported with the use of nativezone in ultra rapid opiate detoxification programs. No causal relationship between natifications and these deaths has been established (see MARNINGS).
Laboratery Fasts: With the exception of liver lest abnormalities (see WARNINGS).

attributed to treatment with nattrexone. Ideopathic thrombocytopenic purpura was reported in one patient who may hae been sensitized to nattrexone in a previous course of treatment with nattrexone. The condition cleared without sequebe after discontinuation of nattrexone and

conticosteroid treatment. ORUG ABUSE AND DEPENDENCE:
ORUG ABUSE AND DEPENDENCE:
Natirezone is a pure opioid artiagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid artiagonist effect is not known to occur.

OVERDOSABCE:

OVERDOSAGE:

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

In the mouse, rat and guines age, the oral LD50 were 1, 100-150 mg/kg; and 1,450 mg/kg; respectively, high doses of natirezone hydrochloride (generally ≥ 1,000 mg/kg) produced salivation, depression/reduced activity, termors, and convulsions. Mortalities in animals due to high-dose natirezone administration usually were due to clonic-toric convulsions and/or respiratory failure.

Transment of previouspe: In view of the lack of actual experience in the treatment of natirezone overdose, patient should be treated symptomatically in a closely supervised environment. Physicians should cortact a poison control center for the most up-to-dask information.

DOSAGE AND ADMINISTRATION:
IF THERE IS ANY OUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST AND DO NOT INITIALE NALIBEZIONE THERPAPY UNTIL THE NALOXONE CHALLENGE IS NEGATIVE.

IN THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A MALLOXONE CHALLENGE TEST AND DO NOT INTIMAL RALIPEXONE THERAPY DIVIT. THE MALLOXONE CHALLENGE IS NEGLOBY A MALLOXONE CHALLENGE IS NEGLOBY AND A dose of 50 mg once daily is recommended for most patients (see indivisitalization of Desage). The placebo-controlled studies that demonstrated the difficacy of natirezone hydrochlorids as an adjunctive treatment of alcoholism used a dose regimen of nativezone hydrochlorids of 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials. A polient in a condidate for instantient with nativezone if.

- The patient is willing to take a medicine to help with alcohol dependence.
- The patient is opioid test for 7-10 days.
- The patient does not have severe or active fiver or kidney problems (Typical guidelines suggest liver function tests no greater than a literate the upper firsts of normal, and biliculain normal).
- The patient is not allargic to nativezone, and no other contraindications are present
- Refer to CONTRAINIOCATIORS, MARNING, and PERCAUTIORS Sections for additional information.

Nativezone should be considered as only one of many factors determining the success of trainment of alcoholism.

Nativezone should be considered as only one of many factors determining the success of trainment, and adjunctive with a good occurrent in the clinical trials with nativezone were the type, intensity, and duration of treatment, appropriate management of commonly-based support groups; and good medication compliance. To achieve the best opassible treatment or common, expectably medication compliance, and and the present of the treatment program, especially medication compliance.

should be implemented for all components of the treatment program, especially medication compliance.

Naturnal of Dipidel Depandence:

Intitiate treatment with neatmenter size the fellowing palelelines:

Intitiate treatment with neatmenter size that the second project free for at least 7-10 days. Self-reporting of abstinence from opicids in opicid addicts should be verified by analysis of the patients unine for absence of opicids. The patient should not be nanifesting withdrawal signs or reporting withdrawal symptoms.

2. If there is any question of occult opicid dependence, perform a reakonone challenge test, if signs of opicid withdrawal are still observed following nationations challenge, tractment with neithersone should not be attempted. The nationone challenge can be repeated in 24 hours.

3. Insatment should be initiated carterfully, with an initial does of 25 mg of nativections hydrochloride. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

Reakones Challenge Test: The nationone challenge test should not be performed in a potient showing clinical signs or symptoms of opicid withdrawal, or in a patient whose urine contains opicids. The nationone challenge test should not be performed in a potient showing clinical signs or with the intervence of the patient should be intitated by whether the intervence or subsequences routes.

symptoms of opioid withdrawal, or in a patient whose urme administered by either the intravenous or subcutaneous routes.

Intravances: Inject 0.2 mg naloxone.
Observe for 30 seconds for signs or symptoms of withdrawal. It no evidence of withdrawal, inject 0.5 mg of naloxone.
Observe for an additional 20 minutes.

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

os, may respond to lower doses of naloxone. In some Note: Individual patients, especially those with opioid dependen cases, 0,1 mg (V naloxone has produced a diagnostic response.

Interpretation of the Challenge: Montor vital signs and observe the patient for signs and symptoms of opioid with-drawal. These may include, but are not firmfael to: nausea, vomiting, dysphoria, yawning, sweating, learing, ninrormea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of lear, sin erytherns, disrupted their patients, fridgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, spuritary distinct, piberscrion; tever, changes in blood pressure, putse or temperature, anxiety, depression, sirribbility, back ache, bone or joint pairs, termons, sensationed of skin crawfung or fraccipitations. If signs or symptoms of withdrawal appear, the test is positive and no additional nalexone should be administered.

Warning. If the jest is country do MQT initiate natinescent therapy. Repeat the challenge in 24 hours. If the lest is negative, natire cone therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold nativersome and repeat the challenge in 24 hours.

Afternative Dozing Scheleles:

Once the patient has been charted on naterzone hydrochloride tablets, 50 mg every 24 hours will produce adequate clinical Once the patient has been charted on naterzone hydrochloride tablets, 50 mg every 24 hours will produce adequate clinical Doctade of the actions of parenterally administrated opioids (i.e., this does will block the effects of a 25 mg intraverous 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 mathrazone 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 nathrazone may be reduced by these

every other day, or 130 mg every wind day. The segment of the days of higher doses and extended dosing intervals.

There may be a higher risk of hepotocellular injury evit single doses above 50 mg, and use of higher doses and extended dosing intervals should be hance the possible risks against the probable benefits (see WARNINGS and CLINICAL PHARNACOLOGY, Clinical Trials, Individualization of Dosside).

Patient Compliance: Matrizense 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.

MOW SUMPLED: Mitresone hydrochloride tablets, 50 mg are supplied as a capsule shaped, white to off-white, film coated tablet, imprinted: (£ 35 on one size and bisected on the other side and are available in bottles of 30 and 100. Storage: Store at 25°C, with brief excursions permitted brivenen 15°C and 30°C (59° - 85°F), controlled room

Storage. Storage at 25 C, with other excursions partificied between temperature, see USP.

KEEP TIGHTLY CLOSED. PROTECT FROM LIGHT.

KEEP THIS AND ALL MEDICATION OUT OF REACH OF CHILDREN

Dispense in tight, light-resistant containers as defined in the USP, with a child resistant closure, as required.

Manufactured by: Eon Labs Manufacturing, Inc. Laurelton, NY 11413

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