PDR®

46 EDITION

1992

PHYSICIANS' DESK REFERENCE®

PDR®

46 EDITION

1992

PHYSICIANS' DESK REFERENCE®

Director of Production:
MARJORIE A. DUFFY

Assistant Director of Production:
CARRIE WILLIAMS

Manager of Production Services:
ELIZABETH H. CARUSO

Format Editor:
MILDRED M. SCHUMACHER

Production Coordinator:
ELIZABETH A. KARST

Art Associate:
JOAN K. AKERLIND

Medical Consultant:
LOUIS V. NAPOLITANO, MD

Product Manager:
JOHN A. MALCZYNSKI

Sales Manager:
CHARLIE J. MEITNER

Account Managers:
CHAD E. ALCORN
MICHAEL S. SARAJIAN
JOANNE C. TERZIDES

Commercial Sales Manager:
ROBIN B. BARTLETT

Direct Marketing Manager:
ROBERT W. CHAPMAN

Manager, Professional Data:
MUKESH MEHTA, R.Ph.

Index Editor:
ADELE L. DOWD

Officers of Medical Economics Data, a division of Medical Economics Company Inc.: President and Chief Executive Officer: Norman R. Snesil; Senior Vice President and Chief Financial Officer: Joseph T. Deithorn; Senior Vice President of Business Development, Stephen J. Sorkenn; Senior Vice President of Operations: Mark L. Weinstein; Vice President, Sales and Marketing: Thomas F. Rice; Vice President of Circulation: Scott I. Rockman; Vice President of Information Services: Edward J. Zecchini.

ISBN 1-56363-003-6

ing high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.
Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.
Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.
Dosage for Concomitant Therapy
Some patients who do not respond to anticholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.
When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.
When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of development of side effects may possibly regain lost benefit with the addition of SYMMETREL.
Dosage for Drug-Induced Extrapyramidal Reactions:
Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.
Dosage for Prophylaxis of Influenza A Virus Illness and Treatment of Uncomplicated Influenza A Virus Illness:
Normal Renal Function:
Adult: The adult daily dosage of SYMMETREL (amantadine hydrochloride) is 200 mg: two 100 mg capsules (or four teaspoonfuls of syrup) as a single daily dose, or the daily dosage may be split into one capsule of 100 mg (or two teaspoonfuls of syrup) twice a day. If central nervous system effects develop on once-a-day dosage, a split dosage schedule may reduce such complaints. In persons 65 years of age or older, the daily dosage of SYMMETREL is 100 mg.
Children: 1 yr.–9 yrs. of age: The total daily dose should be calculated on the basis of 2 to 4 mg/lb/day (4.4 to 8.8 mg/kg/day), but not to exceed 150 mg per day.
9 yrs.–12 yrs. of age: The total daily dose is 200 mg given as one capsule of 100 mg (or two teaspoonfuls of syrup) twice a day.
Impaired Renal Function: Depending upon creatinine clearance, the following dosage adjustments are recommended:

CREATININE CLEARANCE (ml/min./1.73m²)	SYMMETREL DOSAGE
30–50	200 mg 1st day and 100 mg each day thereafter
15–29	200 mg 1st day followed by 100 mg on alternate days
<15	200 mg every 7 days

The recommended dosage for patients on hemodialysis is 200 mg every 7 days.
Prophylactic dosing should be started in anticipation of an influenza A outbreak and before or after contact with individuals with influenza A virus respiratory tract illness.
SYMMETREL should be continued daily for at least 10 days following a known exposure. If SYMMETREL is used chemoprophylactically in conjunction with inactivated influenza A virus vaccine until protective antibody responses develop, then it should be administered for 2 to 3 weeks after the vaccine has been given. When inactivated influenza A virus vaccine is unavailable or contraindicated, SYMMETREL should be administered for up to 90 days in case of possible repeated and unknown exposures. Treatment of influenza A virus illness should be started as soon as possible, preferably within 24 to 48 hours, after onset of signs and symptoms, and should be continued for 24 to 48 hours after the disappearance of signs and symptoms.

HOW SUPPLIED

SYMMETREL (amantadine hydrochloride) is available as capsules (each red, soft gelatin capsule contains 100 mg amantadine hydrochloride) in:
Bottles of 100 NDC 0056-0105-70
Bottles of 500 NDC 0056-0105-85
Hospital Unit-Dose Blister Package of 100 NDC 0056-0105-75
As a syrup (each 5 mL (1 teaspoonful) contains 50 mg amantadine hydrochloride) in:
16 oz. (480 mL) bottles NDC 0056-0205-16.
Store at controlled room temperature (59°–86°F, 15°–30°C).
CAPSULES MANUFACTURED BY
R.P. Scherer—North America
St. Petersburg, Florida 33702
FOR
Du Pont Pharmaceuticals
Wilmington, Delaware 19880
SYMMETREL® is a Registered Trademark of The Du Pont Merck Pharmaceutical Co.
6043-21/Rev. June 1988

TREXAN™ ℞

[treks'an]
(naltrexone hydrochloride)

DESCRIPTION

TREXAN (naltrexone hydrochloride), an opioid antagonist, is a synthetic congener of oxymorphone, and is technically, therefore, a thebaine derivative. However, it has no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. TREXAN (naltrexone hydrochloride) is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone (NARCAN®).
TREXAN (naltrexone hydrochloride) is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/cc. TREXAN is available in scored tablets containing 50 mg of naltrexone hydrochloride.
TREXAN Tablets also contain: alginic acid, FD&C Yellow 6, microcrystalline cellulose, stearic acid, and sugar.

CLINICAL PHARMACOLOGY

Pharmacodynamic actions: TREXAN (naltrexone hydrochloride) is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids. [In this context, the term opioid is used to describe 1) classic morphine-like agonists and 2) analgesics possessing agonist and antagonist activity (e.g., butorphanol, nalbuphine and pentazocine).]
When co-administered with morphine, on a chronic basis, TREXAN blocks the physical dependence to morphine and presumably other opioids.
TREXAN 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 TREXAN is not associated with the development of tolerance or dependence.
In subjects physically dependent on opioids, TREXAN will precipitate withdrawal symptomatology.
Clinical studies indicate that 50 mg of TREXAN 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 TREXAN provides blockade for 48 hours, and tripling the dose of TREXAN provides blockade for about 72 hours.
While the mechanism of action is not fully understood, the preponderance of evidence suggests that TREXAN 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.
Bioavailability/Pharmacokinetics: Following oral administration, TREXAN (naltrexone hydrochloride) is subject to extensive "first pass" hepatic metabolism (its major route of elimination) with approximately 95% of the absorbed drug being converted to several metabolites. The major metabolite, 6-β-naltrexol, like TREXAN, is believed to be a pure antagonist and may contribute to the pharmacological blockade of opioid receptors. A minor metabolite is 2-hydroxy-3-methoxy-6-β-naltrexol. TREXAN and its metabolites are also conjugated to form additional metabolic products. TREXAN and its metabolites are excreted primarily by the kidney, with fecal excretion being a minor elimination pathway. The urinary excretion of unchanged TREXAN accounts for less than 1% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for approximately 38% of an oral dose. The pharmacokinetic profile of TREXAN suggests that TREXAN and its metabolites undergo enterohepatic recycling.
Following the administration of 50 mg TREXAN tablets to 24 healthy adult male volunteers, the C_{max} for TREXAN and its major metabolite, 6-β-naltrexol were 8.6 ng/mL and 99.3 ng/mL, respectively. The maximum concentration (C_{max}), area under the curve (AUC), and amount excreted in the urine for both TREXAN and 6-β-naltrexol increased proportionally as the amount of TREXAN administered increased from 50 mg to 200 mg. The time to maximum concentration (T_{max}) is one hour for both TREXAN and 6-β-naltrexol. The mean elimination half-life ($T\text{-}\frac{1}{2}$) values for TREXAN and 6-β-naltrexol are 3.9 hours and 12.9 hours, respectively. The mean elimination half-life ($T\text{-}\frac{1}{2}$) and time to maximum concentration (T_{max}) for TREXAN and 6-β-naltrexol are independent of dose. TREXAN does not accumulate during chronic dosing. As predicted by its longer half-life, plasma levels of 6-β-naltrexol increase by 40% during chronic TREXAN dosing.
The total body clearance of TREXAN is 1.5 L/min, which approximates liver blood flow, and suggests TREXAN is a highly extracted compound. A renal clearance of 127 mL/min for TREXAN suggests it is solely cleared by glomerular filtration. A renal clearance of 283 mL/min for 6-β-naltrexol suggests an additional renal tubular secretory mechanism.
The volume of distribution for TREXAN following intravenous administration is estimated to be 1350 liters. In vitro tests with human plasma show TREXAN to be 21% bound to plasma protein over the therapeutic dose range.
In a relative bioavailability study in 24 healthy adult male volunteers, TREXAN tablets were found to be bioequivalent to TREXAN syrup; no differences were observed for C_{max}, AUC, and urinary excretion. As expected, the time to maximum concentration (T_{max}) occurred slightly earlier for the syrup (0.6 hours) than for the tablet (1.0 hr).

INDICATIONS AND USAGE

TREXAN (naltrexone hydrochloride) is indicated to provide blockade of the pharmacologic effects of exogenously administered opioids as an adjunct to the maintenance of the opioid free-state in detoxified formerly opioid-dependent individuals.
There are no data that demonstrate an unequivocally beneficial effect of TREXAN on rates of recidivism among detoxified, formerly opioid-dependent individuals.

CONTRAINDICATIONS

TREXAN is contraindicated in:
1) Patients receiving opioid analgesics.
2) Opioid dependent patients.
3) Patients in acute opioid withdrawal (see WARNINGS).
4) Any individual who has failed to pass the NARCAN challenge (see DOSAGE AND ADMINISTRATION section).
5) Any individual who has a positive urine screen for opioids.
6) Any individual with a history of sensitivity to TREXAN (naltrexone hydrochloride). It is not known if there is any cross-sensitivity with naloxone or other phenanthrene containing opioids.
7) Any individual with acute hepatitis or liver failure.

WARNINGS

Hepatotoxicity:

TREXAN has the capacity to cause dose related hepatocellular injury.
Prior to making a decision to initiate treatment with TREXAN, the physician should establish whether the patient has subclinical liver injury or disease. (See PRECAUTIONS; Laboratory Tests.) TREXAN is contraindicated in acute hepatitis or liver failure, but its use even in patients with evidence of less severe liver disease or a history of recent liver disease must be carefully considered in light of its hepatotoxic potential.
The evidence that identified TREXAN as a hepatotoxin was not obtained in studies involving its use at the doses recommended for opiate blockade, where the changes in serum levels of liver enzymes seen were similar to those present at baseline in the study population. However, the margin of separation between the apparently safe and the hepatotoxic doses appears to be only five-fold or less.

Evidence of TREXAN's hepatotoxic potential is derived primarily from a placebo controlled study in which TREXAN was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In the study, 5 of 26 TREXAN recipients developed elevations of serum transaminases (i.e., peak SGPT 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 TREXAN is a direct (i.e., not an idiosyncratic) hepatotoxin. This conclusion is also supported by evidence from other placebo controlled studies in which exposure to TREXAN at doses from one to two-fold the amount recommended for opiate blockade consistently produced more numerous and more significant elevations of serum transaminases than did placebo, and reports of transaminase elevations in 3 of 9 patients with Alzheimer's Disease who received TREXAN (up to 300 mg/day) for 5 to 8 weeks in a open clinical trial.
Unintended Precipitation of Abstinence: To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing sub-clinical abstinence syndrome, patients should remain opioid-free for a minimum of 7–10 days before starting TREXAN. Since the absence of an opioid drug in the

Continued on next page

Du Pont Multi-Source—Cont.

urine is often not sufficient proof that a patient is opioid-free, a NARCAN challenge should be employed to exclude the possibility of precipitating a withdrawal reaction following administration of TREXAN. The NARCAN challenge test is described in the DOSAGE AND ADMINISTRATION section.

While TREXAN is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by TREXAN 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 surmounting the opiate blockade. See Information for Patients section.

PRECAUTIONS

General:

Actions Suggested When Reversal of TREXAN Blockade is Required: In an emergency situation requiring analgesia which can only be achieved with opioids, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. No methods to reverse overdose have been established by controlled clinical trials; therefore in such circumstances, a rapidly acting analgesic which minimizes respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient.

Additionally, non-receptor mediated actions may occur (e.g., facial swelling, itching, generalized erythema presumably due to histamine release).

Irrespective of the drug chosen to reverse TREXAN (naltrexone hydrochloride) blockade, the patient should be monitored closely by appropriately trained personnel in a hospital setting.

Actions Suggested When Withdrawal is Accidentally Precipitated With TREXAN: Severe opioid withdrawal syndromes precipitated by the accidental ingestion of TREXAN have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of TREXAN 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 tailored to meet individual requirements.

Interference With the Action of Narcotic Containing Drug Product: Patients taking TREXAN may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. Where a non-opioid containing alternative is available, it should be used.

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

You have been prescribed TREXAN (naltrexone hydrochloride) as part of the comprehensive treatment for your drug dependence. You should carry identification to alert medical personnel to the fact that you are taking TREXAN. A TREXAN 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 TREXAN therapy.

You should take TREXAN 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.

Laboratory tests: Tests designed to detect hepatic injury should be obtained prior to initiation of TREXAN therapy and periodically thereafter. (See WARNINGS section on Hepatotoxicity.)

Periodic testing of all patients after initiation of treatment is critical if the occurrence of TREXAN induced liver damage is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are of use; thereafter, clinical judgment about the frequency of monitoring must be relied upon.

Laboratory tests which may be used for the separation and detection of morphine, methadone or quinine in the urine and with which TREXAN does not interfere include thin-layer, gas-liquid, and high pressure liquid chromatographic methods.

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: TREXAN (100 mg/kg, approximately 140 times the human therapeutic dose) caused a significant increase in pseudopregnancy 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. TREXAN 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 TREXAN (100 mg/kg) prior to and throughout gestation, and rabbits treated with 60 mg/kg of TREXAN during the period of organogenesis.

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

LABOR AND DELIVERY

Whether or not TREXAN affects the duration of labor and delivery is unknown.

NURSING MOTHERS

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

PEDIATRIC USE

The safe use of TREXAN in subjects younger than 18 years old has not been established.

ADVERSE REACTIONS

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

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

TREXAN used at the doses recommended to produce opiate receptor blockade does *not* appear to be the cause of any of the numerous adverse events and abnormal laboratory findings, *including liver function abnormalities*, that were observed in the course of the clinical trials that enrolled individuals with a history of both alcohol and substance abuse. In the one placebo controlled trial intended to assess the effects of opiate receptor blockade on drug abuse recidivism, observed untoward events and laboratory abnormalities occurred with nearly equal frequency among placebo and TREXAN recipients. In all open studies, the untoward events observed (e.g., lymphocytosis, transaminase elevations, GI disturbances) were findings that would be anticipated in any similar population not treated with naltrexone. Supporting this judgment, many of the abnormalities detected during the course of the clinical trials were present at baseline, and in some instances, baseline abnormalities, including transaminase elevations, improved or returned to normal during the course of treatment with naltrexone.

In summary, among opioid free individuals, TREXAN 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, TREXAN may cause serious reactions (see CONTRAINDICATIONS, WARNINGS, DOSAGE AND

Events other than hepatocellular injury reported during clinical testing:

The following adverse reactions have been reported both at baseline and during the TREXAN medication period at an incidence rate of more than 10%:

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

The incidence was less than 10% for:

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

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

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

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

Gastrointestinal: excessive gas, hemorrhoids, diarrhea, ulcer.

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

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

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

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

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

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

Lethargy and somnolence have been reported following dosing of TREXAN (naltrexone hydrochloride) and thioridazine.

Laboratory tests: With the exception of liver test abnormalities in investigator studies (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 TREXAN.

In the trials evaluating TREXAN for the blockade of opiate receptors, abnormal liver function tests and lymphocytosis were the two most common categories of abnormalities reported. As noted earlier, these abnormalities are common among populations of parenteral opioid users and alcoholics. As is the case with the untoward events described above, a large proportion of patients had abnormal laboratory tests at baseline, further supporting the conclusion that the abnormalities observed are not attributable to TREXAN.

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

DRUG ABUSE AND DEPENDENCE

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

In the mouse, rat and guinea pig, the oral LD_{50}s were 1,100 $\pm$ 96 mg/kg; 1,450 $\pm$ 265 mg/kg; and 1,490 $\pm$ 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

Consideration should be given to contacting a poison control center for the most up-to-date information.

In view of the lack of actual experience in the treatment of TREXAN overdose, patients should be treated symptomatically in a closely supervised environment.

DOSAGE AND ADMINISTRATION

Induction of TREXAN Therapy: DO NOT ATTEMPT TREATMENT UNTIL NARCAN CHALLENGE IS NEGATIVE (see below). Initiate treatment with TREXAN using the following guidelines:

1. Treatment should not be attempted until the patient has remained opioid-free for 7–10 days. Self-reporting of abstinence from opioids 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. A NARCAN challenge test (see below) should be administered to the patient. If signs of opioid withdrawal are still observed following NARCAN challenge, treatment with TREXAN should not be attempted. The NARCAN chal-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.