NALTREXONE (Systemic)

Introduction

Revised: 08/13/97

Interim revision: 07/07/98

VA CLASSIFICATION (Primary/Secondary)¾AD800/AD100
Commonly used brand name(s):ReVia.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Opioid (narcotic) antagonist; opioid (narcotic) abuse therapy adjunct; alcohol abuse therapy adjunct.

Indications

Accepted

Opioid (narcotic) drug use, illicit (treatment adjunct) 1, 2, 3, 4, 5, 6, 16, 24, 25, 26, 27¾Naltrexone is indicated as an adjunct to other measures, including psychological and social counseling, in the treatment of detoxified, formerly opioid-dependent individuals. Naltrexone assists in maintaining an opioid-free state in these individuals; however, an unequivocally beneficial effect on recidivism rates has not been demonstrated.

Alcoholism (treatment) 1, 2, 7, 8, 9, 10, 11, 12, 13, 14¾Naltrexone is indicated as an adjunct to other measures, including psychological and social counseling, in the treatment of alcohol dependence.

Unaccepted

Naltrexone is not effective in treating dependency on cocaine or other nonopioid drugs 26.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Naltrexone: 341.41 15

Mechanism of action/Effect:

Naltrexone binds to opioid receptors in the central nervous system (CNS) and competitively inhibits the actions of opioid drugs (both pure agonists and agonist/antagonists) and endogenous opioids 1, 2, 16.

Naltrexone markedly attenuates or completely blocks opioid-induced euphoria and physical dependence; with continued use it may therefore reduce the patient's craving for opioid drugs.

Naltrexone may be more effective in blocking the subjective effects (such as euphoria) than the objective effects (such as respiratory depression or miosis) of opioids [1, 28].

The mechanism of action whereby naltrexone reduces alcohol craving and consumption is not completely understood [34].

Naltrexone may attenuate alcohol-induced euphoria, thereby reducing the patient's craving for alcohol [1, 2, 34].

Other actions/effects:

Naltrexone precipitates withdrawal symptoms in individuals who are physically dependent on opioid drugs [1, 2].

It also blocks the therapeutic (e.g., analgesic, antidiarrheal, and antitussive) actions of opioids [1, 2].

Although naltrexone has few if any actions other than opioid blockade, it produces some pupillary constriction via an unknown mechanism [1].

Absorption:

Rapid and almost complete [1, 2, 16, 17].

Protein binding:

Low (21%) [1, 2, 16, 17].

Biotransformation:

Hepatic; approximately 98% of a dose is metabolized [1, 2, 16, 17].

Naltrexone is subject to extensive first-pass hepatic metabolism. The major metabolite, 6-beta-naltrexol, has opioid antagonist activity and may contribute to the therapeutic effect [1, 2, 16, 17].

Half-life:

Elimination¾
Naltrexone: Approximately 4 hours; independent of dose [1, 2, 16, 17].

6-Beta-naltrexol: Approximately 13 hours; independent of dose [1, 2, 16, 17].

Time to peak concentration:

For both naltrexone and 6-beta-naltrexol¾1 hour; independent of dose [1, 2, 16, 17].

Peak serum concentration:

Following a single 50-mg dose¾
Naltrexone: 8.6 nanograms per mL [2].

6-Beta-naltrexol: 99.3 nanograms per mL [2].

Note: Naltrexone and 6-beta-naltrexol do not accumulate with long-term administration of 100 mg of naltrexone a day [1, 2].

Duration of action:

Dose-dependent; as determined by blockade of the effects of 25 mg of intravenously administered heroin¾

50-mg dose: 24 hours [1, 2, 16, 17].

100-mg dose: 48 hours [1, 2, 16, 17].

150-mg dose: 72 hours [1, 2, 16, 17].

Elimination:

Primarily renal; 60% of a dose is excreted in the urine within 48 hours. Less than 2% of a dose is excreted in the urine as unchanged naltrexone; about 43% of a dose is excreted as unchanged or conjugated 6-beta-naltrexol [1].

Precautions to Consider

Carcinogenicity/Tumorigenicity

Studies in rats have shown that naltrexone caused small increases in the numbers of mesotheliomas in males and tumors of vascular origin in both sexes. However, only the incidence of vascular tumors in females (4%) exceeded the maximum (2%) reported in historical control groups [1].

Mutagenicity

Naltrexone produced weakly positive findings in the Drosophila recessive lethal assay and in nonspecific DNA repair tests with E. coli[1].

However, no positive findings were reported in 20 other tests using bacterial, mammalian, and tissue culture systems [1].

The significance of these findings is not known.

Pregnancy/Reproduction

Fertility¾Studies in rats given doses of 100 mg per kg (approximately 100 times the human therapeutic dose) have shown that naltrexone causes a significant increase in pseudopregnancy and a decrease in the pregnancy rate of mated females [1].

The relevance of these findings to humans is not known [1].

Pregnancy¾Adequate and well-controlled studies in humans have not been done [1].

Naltrexone has been shown to have embryocidal and fetotoxic effects in rats (doses of 30 times the human dose equivalent prior to and throughout gestation) and rabbits (doses of 60 times the human dose equivalent during the period of organogenesis) [1].

FDA Pregnancy Category C 1.

Breast-feeding

It is not known whether naltrexone is distributed into breast milk 1, 2.

However, problems in humans have not been documented 1.

Pediatrics

Appropriate studies on the relationship of age to the effects of naltrexone have not been performed in the pediatric population. However, no pediatrics-specific problems have been documented 1, 2.

Geriatrics

Appropriate studies on the relationship of age to the effects of naltrexone have not been performed in the geriatric population. However, no geriatrics-specific problems have been documented 1, 2.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications also interact with this medication.
Hepatotoxic medications 1, 2 (see Appendix II)

(additive hepatotoxicity may occur)

>> Opioid (narcotic) medications 1, 2

(administration of naltrexone to a patient physically dependent on opioid drugs will precipitate withdrawal symptoms; symptoms may appear within 5 minutes of naltrexone administration, persist for up to 48 hours, and be difficult to reverse; opioid-dependent patients should be detoxified before treatment with naltrexone; a naloxone challenge test usually is administered before naltrexone therapy is started to verify abstinence [see General Dosing Information])
(naltrexone blocks the therapeutic effects of opioids [i.e., analgesic, antidiarrheal, and antitussive]; naltrexone therapy should not be initiated in patients receiving these agents for therapeutic purposes; also, patients receiving naltrexone should be advised to use alternative medications when necessary)
(administration of increased doses of opioids to override naltrexone-induced blockade of opioid receptors may result in increased and more prolonged respiratory depression and/or circulatory collapse)
(naltrexone should be discontinued several days prior to elective surgery if administration of an opioid medication prior to, during, or following surgery is unavoidable)
(the efficacy of naltrexone in antagonizing opioid effects not mediated via opioid receptors [i.e., those which may be caused by histamine release, such as facial swelling, itching, generalized erythema, hives, and, to some extent, hypotension] has not been fully determined; naltrexone may not antagonize these effects completely)

Thioridazine

(lethargy and somnolence have been reported rarely when patients taking thioridazine have begun naltrexone therapy 21, 22, 23)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Serum transaminase (ALT [SGPT]; AST [SGOT]) activity 1, 2, 33

(excessive doses of naltrexone may cause hepatocellular damage in a dose-dependent manner; elevation of serum transaminase activity may occur; although mild abnormalities occur frequently in patients with alcohol or drug addiction, and are not necessarily related to naltrexone-induced hepatotoxicity, significant abnormalities indicative of the medication's hepatotoxic potential have occurred in subjects receiving about five times the recommended daily dose; in one placebo-controlled study, 5 of 26 subjects developed elevations of serum transaminases 3 to 19 times the baseline value 2 ; the abnormalities were reversible upon discontinuation of naltrexone, and symptomatic hepatotoxicity with clinical use has not been reported)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Allergic reaction to naltrexone, history of 1, 2

>> Dependence on opioid drugs, current, as demonstrated by presence of withdrawal symptoms, detection of opioid drugs in urine, or failure to pass naloxone challenge test 1, 2

(naltrexone will precipitate or exacerbate withdrawal symptoms)

>> Hepatic failure or

>> Hepatitis, acute

(increased risk of hepatotoxicity 1, 2)

Risk-benefit should be considered when the following medical problems exist

>> Hepatic disease, current or recent history of, excluding mild liver function abnormalities known to be associated with opioid or alcohol dependence

(increased risk of hepatotoxicity 1, 2 ; naltrexone may cause hepatocellular damage in a dose-dependent manner 1, 2)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Hepatic function tests

(recommended prior to initiation of therapy to detect hepatic injury and/or to determine baseline values, then periodically thereafter; naltrexone should be discontinued if significant abnormalities occur)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Skin rash 1, 2, 16
Incidence rare

Blurred vision or aching, burning, or swollen eyes 1, 2; chest pain 1, 2; confusion 1, 2, 5, 16; discomfort while urinating and/or frequent urination 1, 2, 5; edema 1, 2 swelling of face, fingers, feet, or lower legs 1, 2); weight gain); fever 1, 2; gastrointestinal ulceration 1, 2, 26 abdominal or stomach pain, severe); hallucinations 1, 2; increased blood pressure 1, 2, 16; itching 1, 2; mental depression or other mood or mental changes 1, 2, 16, 19; ringing or buzzing in ears 1, 2; shortness of breath 1, 2
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal cramping or pain, mild to moderate 1, 2, 5, 16, 26; anxiety, nervousness, restlessness, and/or trouble in sleeping 1, 2, 16, 18; headache 1, 2, 18; joint or muscle pain 1, 2; nausea or vomiting 1, 2, 5, 16, 18, 26; unusual tiredness 1, 2, 21, 22, 23
Incidence less frequent or rare

Chills 1, 2; constipation 1, 2; cough 1, 2; diarrhea 1, 2; dizziness 1, 2; fast or pounding heartbeat 1, 2; hoarseness 1, 2; increased thirst 1, 2; irritability 1, 2, 16; loss of appetite 1, 2, 16, 26; runny or stuffy nose 1, 2; sexual problems in males 1, 2; sinus problems 1, 2; sneezing 1, 2; sore throat 1, 2

Note: In some individuals, loss of appetite has led to substantial weight loss requiring discontinuation of therapy.
Some of the above-listed side/adverse effects are identical to symptoms of opioid withdrawal (see list below). Several of them, such as abdominal pain, anxiety, joint or muscle pain, nausea or vomiting, and unusual tiredness, may lessen or disappear during continued use. It has been suggested that such effects may be mild withdrawal symptoms in some patients.

Those indicating possible withdrawal in patients physically dependent on opioid drugs

Note: These side effects may occur within 5 minutes after administration of naltrexone and may persist for up to 48 hours.Abdominal or stomach cramps 1, 2; anxiety, nervousness, restlessness, or irritability 1, 2; diarrhea 1, 2; fast heartbeat 1, 2; fever, continuing runny nose, or sneezing 1, 2; gooseflesh 1, 2; increased sweating 1, 2; increased yawning 1, 2; joint or muscle pain 1, 2; loss of appetite 1, 2; nausea or vomiting 1, 2; shivering or trembling 1, 2; trouble in sleeping 1, 2; weakness 1, 2

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

Clinical experience with overdose is lacking. It is recommended that the patient be closely monitored and the observed symptoms treated as required.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Naltrexone (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Allergic reaction to naltrexone, history of
Other medications, especially opioids
Other medical problems, especially hepatic failure; hepatitis, acute; or other hepatic disease
Proper use of this medication

>> Importance of taking each dose as scheduled

>> Proper dosing
Missed dose: If dosing schedule is¾
One tablet every day¾
Taking as soon as possible; not taking if not remembered until the next day; not doubling the next day's dose

One tablet every weekday and two tablets on Saturday¾
If weekday dose missed¾Following missed dose directions as for one tablet every day
If Saturday dose missed¾Taking two tablets as soon as possible if remembered the same day, or taking one tablet if not remembered until Sunday, then returning to regular dosing schedule on Monday

Two tablets every other day¾
Taking two tablets as soon as remembered, skipping a day, then continuing every other day; or
Taking two tablets as soon as possible if remembered the same day, or taking one tablet if not remembered until the next day, then returning to the regular dosing schedule

Two tablets on Monday and Wednesday and three tablets on Friday¾

If Monday or Wednesday dose missed¾Taking two tablets as soon as possible if remembered the same day, or taking one tablet if not remembered until the next day, then returning to the regular dosing schedule

If Friday dose missed¾Taking three tablets as soon as possible if remembered the same day; taking two tablets if not remembered until Saturday or one tablet if not remembered until Sunday; returning to the regular dosing schedule on Monday

Three tablets every three days¾

Taking three tablets as soon as remembered, skipping two days, then continuing every three days; or

Taking three tablets as soon as possible if remembered the same day; taking two tablets if not remembered until the next day, or one tablet if not remembered until the following day, then returning to the regular dosing schedule

>> Proper storage

Precautions while using this medication

>> Regular visits to physician or clinic; blood tests may be needed to detect possible hepatotoxicity

>> Importance of compliance with all components of a comprehensive treatment program, including attending counseling sessions and/or support group meetings; naltrexone is intended only as an aid to other forms of therapy that discourage return to alcohol or opioid use

>> Not attempting to overcome effects of naltrexone by taking opioids; such attempts may lead to coma or death; therapy with naltrexone may lead to increased sensitivity to the effects of narcotics

>> Not using opioid medications to relieve pain, diarrhea, or cough because naltrexone also prevents therapeutic effects of opioids

>> Not taking naltrexone to perform activities (for example, driving) while under the influence of alcohol

>> Never sharing medication with others, especially those dependent on opioids

>> Notifying all physicians, dentists, and pharmacists of use of naltrexone

>> Carrying identification card indicating use of medication

Side/adverse effects

Signs of potential side effects, especially skin rash; blurred vision or aching, burning, or swollen eyes; chest pain; confusion; discomfort while urinating and/or frequent urination; edema; fever; gastrointestinal ulceration; hallucinations; itching; mental depression or other mood or mental changes; ringing or buzzing in ears; shortness of breath

General Dosing Information

When naltrexone is used as adjunct therapy to treat opioid (narcotic) abuse, naltrexone therapy should not be initiated until the patient has been completely detoxified, is free of withdrawal symptoms, and has remained opioid-free for 7 to 10 days (following use of a relatively short-acting opioid such as heroin) or longer (following use of a longer-acting opioid such as methadone) 1, 2.

Abstinence should be verified by examination of the urine for opioids and/or a naloxone challenge test [1, 2].

Clonidine or methadone may be used to prevent or attenuate withdrawal symptoms during detoxification [24, 25, 30, 31]; however, if methadone is used, initiation of naltrexone therapy must be delayed until there is no risk of precipitating withdrawal symptoms [1, 2].

The naloxone challenge test should not be administered if withdrawal symptoms are present or the patient's urine contains opioids [1, 2].

Naloxone may be administered intravenously or subcutaneously. If the intravenous route is used, an initial dose of 200 mcg (0.2 mg) should be administered and the patient observed for 30 seconds for withdrawal symptoms; if none occurs, an additional 600 mcg (0.6 mg) of naloxone should be administered and the patient observed for 20 minutes [1, 2].

If the subcutaneous route is used, 800 mcg (0.8 mg) of naloxone should be administered and the patient observed for 20 minutes for withdrawal symptoms [1, 2].

If withdrawal symptoms occur, the naloxone challenge should be repeated at 24-hour intervals until absence of opioid dependence is confirmed [1, 2].

It is recommended that naltrexone therapy be initiated with a low dose (e.g., 25 mg), which may be increased to 50 mg a day if no signs or symptoms of withdrawal occur [1, 2].

Alternatives to daily administration include several maintenance dosing regimens permitting administration of higher doses every second or third day on an occasional or regular basis (e.g., over weekends). It has been suggested that less frequent dosing, scheduled to suit the individual patient, may improve compliance [1, 2].

The alternative dosing schedules have not been studied in the treatment of alcoholism [1].

In emergency situations requiring an opioid analgesic, naltrexone's effects can be overcome by administering sufficiently high doses of the analgesic [1, 2].

It is recommended that a rapidly acting analgesic with minimal potential for respiratory depression be administered in doses carefully titrated to the needs of the patient. Since high doses of analgesic are required, the risk of adverse effects, including severe, prolonged respiratory depression and circulatory collapse, is greatly increased [1, 2, 32].

Therefore, such treatment must be carried out in a hospital setting, where the patient can be carefully monitored by trained personnel. Some patients on naltrexone therapy may be sensitive to low doses of opioids. In these patients, adverse effects may occur even with low doses of opioids [1].

Naltrexone does not cause physical or psychological dependence [1, 2].

Tolerance to the opioid-blocking action of naltrexone has not been reported [1, 2].

Long-term success with naltrexone-based regimens for the treatment of alcoholism or opioid drug dependence has not been established [7, 27].

Compliance may be improved if the medication is administered as a component of an integrated program including psychosocial therapy 11, 14, 18.

For treatment of adverse effects

Precipitation of withdrawal symptoms in physically dependent patients: Symptoms may be very difficult to reverse. It is recommended that the patient be monitored closely and treated for observed symptoms as required.

Oral Dosage Forms

NALTREXONE HYDROCHLORIDE TABLETS

Usual adult dose

Opioid (narcotic) drug use, illicit (treatment adjunct)¾
Initial 1, 2¾
Oral, 25 mg for the first dose; an additional 25 mg may be given one hour later if no withdrawal symptoms occur.

Maintenance 1, 2¾
Oral, 50 mg every twenty-four hours. Alternatively, the weekly dose of 350 mg may be administered using an intermittent dosing schedule, such as:
Oral, 50 mg every twenty-four hours on weekdays and 100 mg on Saturday; or
Oral, 100 mg every forty-eight hours; or
Oral, 100 mg every Monday and Wednesday and 150 mg on Friday; or
Oral, 150 mg every seventy-two hours.
Alcoholism (treatment) 1, 2¾
Oral, 50 mg every twenty-four hours for up to twelve weeks.

Usual pediatric dose

Dosage in patients up to 18 years of age has not been established.

Strength(s) usually available

U.S.¾50 mg (Rx)[ReVia (scored) (lactose) (microcrystalline cellulose) (crospovidone) (colloidal silicon dioxide) (magnesium stearate) (hydroxypropyl methylcellulose) (titanium dioxide) (polyethylene glycol) (polysorbate 80) (yellow iron oxide) (red iron oxide)] [Generic]

Canada¾50 mg (Rx)[ReVia (scored) (lactose monohydrate) (microcrystalline cellulose) (crospovidone) (colloidal silicon dioxide) (magnesium stearate) (microcrystalline methylcellulose) (Pale Yellow OpadryÒ YS-1-6378-G) 2]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight, light-resistant container, unless otherwise specified by manufacturer.