

1. NAME OF THE MEDICINE

Naltrexone 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg of naltrexone hydrochloride.

Excipients with known effect: Lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.

Naltrexone is presented as beige, film-coated, capsule-shaped tablets, with a score on each side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Naltrexone is indicated for use within a comprehensive treatment programme for alcohol dependence.

Naltrexone is also indicated as adjunctive therapy in the maintenance of formally opioid-dependent patients who have ceased the use of opioids such as diamorphine (heroin) and morphine.

4.2 Dose and method of administration

Therapy may only be initiated by a specialist with experience in alcohol and drug dependence management.

Do not attempt treatment with naltrexone hydrochloride unless, in the medical judgement of the prescribing physician, there is no reasonable possibility of opioid use within the past 7-10 days. If there is any question of occult opioid dependence, perform a NARCAN challenge test and do not initiate naltrexone hydrochloride therapy until the NARCAN challenge is negative.

Treatment of Alcohol Dependence

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

A patient is a candidate for treatment with naltrexone hydrochloride if:

- the patient is willing to take a medicine to help with alcohol dependence
- the patient is opioid free for 7-10 days
- the patient does not have severe or active liver or kidney problems (typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal.)
- the patient is not allergic to naltrexone hydrochloride, and no other contraindications

are present.

Refer to Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use for additional information.

Naltrexone hydrochloride should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with naltrexone hydrochloride were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment programme, especially medication compliance. The duration of treatment should not exceed 3 months.

Treatment of Opioid Dependence

Initiate treatment with naltrexone hydrochloride using the following guidelines:

1. Treatment should not be attempted unless the patient has remained opioid-free for at least 7- 10 days. Self-reporting of abstinence from opioids in opioid addicts should be verified by analysis of the patient's urine for absence of opioid. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.
2. If there is any question of occult opioid dependence, perform a NARCAN challenge test. If signs of opioids withdrawal are still observed following NARCAN challenge, treatment with naltrexone hydrochloride should not be attempted. The NARCAN challenge can be repeated in 24 hours.
3. Treatment should be initiated carefully, with an initial dose of 25 mg of naltrexone hydrochloride. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

NARCAN Challenge Test

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

Intravenous:

- Inject 0.2 mg NARCAN.
- Observe for 30 seconds for signs or symptoms of withdrawal.
- If no evidence of withdrawal, inject 0.6 mg of NARCAN.
- Observe for an additional 20 minutes.

Subcutaneous:

- Administer 0.8 mg NARCAN.
- Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of NARCAN. In some cases, 0.1 mg IV NARCAN has produced a diagnostic response.

Interpretation of the Challenge

Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhoea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood

pressure, pulse or temperature, anxiety, depression, irritability, back ache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional NARCAN should be administered.

Warning: If the test is positive, do NOT initiate naltrexone hydrochloride therapy. Repeat the challenge in 24 hours. If the test is negative, naltrexone hydrochloride may be started if no other contraindications are present. If there is any doubt about the result of the test, hold naltrexone hydrochloride and repeat the challenge in 24 hours.

Alternative Dosing Schedules

Once the patient has been started on naltrexone hydrochloride, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (i.e. this dose will block the effects of a 25 mg intravenous heroin challenge). Dosage increase and/or a flexible dosing regimen may be appropriate in some cases. The degree of blockade produced by naltrexone hydrochloride may be reduced by extended dosing intervals.

There may be a higher risk of hepatocellular injury with single doses above 50 mg, and use of higher doses and extended dosing intervals should balance the possible risks against the probable benefits (see Section 4.4 Special warnings and precautions for use).

Patient compliance:

Naltrexone hydrochloride 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 programme, including medication compliance.

As patient motivation and social support are likely to influence treatment outcomes, this makes patient selection an important clinical responsibility.

4.3 Contraindications

Naltrexone hydrochloride is contraindicated in:

1. Patients receiving opioid analgesics.
2. Patients currently dependent on opioids since an acute withdrawal syndrome may ensue.
3. Patients in acute opioid withdrawal (See Section 4.4 Special warnings and precautions for use).
4. Any individual who has failed the NARCAN challenge test or who has a positive urine screen for opioids.
5. Any individual with a history of sensitivity to naltrexone hydrochloride or any other components of this product. It is not known if there is any cross-sensitivity with naloxone or the phenanthrene containing opioids.
6. Any individual with acute hepatitis or liver failure. Naltrexone hydrochloride should not be given to patients with acute hepatitis or liver failure.

4.4 Special warnings and precautions for use

General

Hepatotoxicity

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

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

The margin of separation between the apparently safe dose of naltrexone hydrochloride and the dose causing hepatic injury appears to be only five-fold or less.

Naltrexone hydrochloride does not appear to be a hepatotoxin at the recommended doses.

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

Evidence of the hepatotoxic potential of naltrexone hydrochloride is derived primarily from a placebo controlled study in which naltrexone hydrochloride was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day).

In that study, 5 of 26 naltrexone hydrochloride recipients developed elevations of serum transaminases (i.e. peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone hydrochloride is a direct (i.e. not idiosyncratic) hepatotoxin.

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

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

Unintended Precipitation of Abstinence

To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting naltrexone hydrochloride. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a NARCAN challenge should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of naltrexone hydrochloride. The NARCAN challenge test is described in Section 4.2 Dose and method of administration.

Attempt to Overcome Blockade

While naltrexone hydrochloride is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by naltrexone hydrochloride is surmountable. This could be 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). **Patients should be told of the serious consequences of trying to overcome the opioid blockade.**

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). **Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.**

Reversal of naltrexone hydrochloride blockade

In an emergency situation in patients receiving fully blocking doses of naltrexone hydrochloride, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anaesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimises the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalised erythema, or bronchoconstriction) presumably due to histamine release.

Irrespective of the medicine chosen to reverse naltrexone hydrochloride blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Accidentally Precipitated Withdrawal

Severe opioid withdrawal syndromes precipitated by the accidental ingestion of naltrexone hydrochloride have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of naltrexone hydrochloride 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 diarrhoea have required intravenous fluid administration. In all cases patients were closely monitored and therapy with non-opioid medications was tailored to meet individual requirements.

Use of naltrexone hydrochloride does not eliminate or diminish withdrawal symptoms. If naltrexone hydrochloride is initiated early in the abstinence process, it will not preclude the patient's experience of the full range of signs and symptoms that would be experienced if naltrexone hydrochloride had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients:

Renal Impairment

Naltrexone hydrochloride and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.

Hepatic Impairment

Cautions should be exercised when naltrexone hydrochloride is administered to patients with liver disease. An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Suicide

The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with naltrexone hydrochloride (see Section 4.8 Undesirable effects).

Use in Children

The safe use of naltrexone hydrochloride in paediatric patients younger than 18 years old has not been established.

Laboratory Tests

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

4.5 Interaction with other medicines and other forms of interaction

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

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

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

Patients taking naltrexone hydrochloride may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrhoeal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient receiving naltrexone hydrochloride, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged (see Section 4.4 Special warnings and precautions for use).

Interactions with Laboratory Tests

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Use in pregnancy Category B3

The following includes statements based on the results of experiments in rats, which do not form appreciable quantities of the major human metabolite, 6- β -naltrexol. Thus the potential reproductive toxicity of 6- β -naltrexol in rats is not known.

Naltrexone increased the incidence of early foetal loss when administered to rats at oral doses ≥ 30 mg/kg/day (5 times the recommended therapeutic dose, based on surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (18 times the recommended therapeutic dose, based on surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of organogenesis at doses up to 200 mg/kg/day (respectively 32 and 59 times the recommended therapeutic dose, based on surface area).

There are no adequate and well-controlled studies in pregnant women.

Breast-feeding

In animal studies, naltrexone and 6- β -naltrexol were excreted in the milk of lactating rats dosed orally with naltrexone. Whether or not naltrexone hydrochloride is excreted in human milk is unknown. Because many medicines are excreted in human milk, caution should be exercised when naltrexone hydrochloride is administered to a nursing woman.

Fertility

Naltrexone hydrochloride (100 mg/kg PO, 16 times the recommended therapeutic dose, based on surface area) caused a significant increase in pseudo-pregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

4.7 Effects on ability to drive and use machines

Naltrexone hydrochloride may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

4.8 Undesirable effects

During two randomised, doubled-blinded placebo-controlled 12 week trials to evaluate the efficacy of naltrexone hydrochloride as an adjunctive treatment of alcohol dependence, most patients tolerated naltrexone hydrochloride well. In these studies, a total of 93 patients received naltrexone hydrochloride at a dose of 50 mg once daily. Five of these patients discontinued naltrexone hydrochloride because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of naltrexone hydrochloride in detoxified, formally opioid-dependent individuals failed to identify any single, serious untoward risk of naltrexone hydrochloride use, placebo-controlled studies employing up to five-fold higher doses of naltrexone hydrochloride (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that naltrexone hydrochloride causes hepatocellular injury in a substantial proportion of patients exposed at higher doses (see Section 4.4 Special warnings and precautions for use: Laboratory Tests)

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate naltrexone hydrochloride, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid free." It is critical to recognise that naltrexone hydrochloride can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially opioid addiction, are at risk for multiple numerous adverse events and abnormal laboratory findings, **including liver function abnormalities**. Data from both controlled and observational studies suggest that these abnormalities, other than the dose-related hepatotoxicity described above, are not related to the use of naltrexone hydrochloride.

Among opioid free individuals, naltrexone hydrochloride administration at the recommended dose has not been associated with a predictable profile of serious adverse or untoward events. However, as mentioned above, among individuals using opioids, naltrexone hydrochloride may cause serious withdrawal reactions (see Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration).

Adverse events, including withdrawal symptoms and death, have been reported with the use of naltrexone hydrochloride in ultra rapid detoxification programmes. No causal relationship

between naltrexone hydrochloride and these deaths has been established. (see Section 4.4 Special warnings and precautions for use).

Reported Adverse Events

Naltrexone hydrochloride has not been shown to cause significant increases in complaints in placebo- controlled trials in patients known to be free of opioids for more than 7-10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints (see Section 4.2 Dose and method of administration).

Alcohol Dependence

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone hydrochloride, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

RATE RANGES OF NEW ONSET EVENTS		
	Naltrexone	Placebo
Depression	0-15%	0-17%
Suicide Attempt/Ideation	0-1%	0-3%

Although no casual relationship with naltrexone hydrochloride is suspected, physicians should be aware that treatment with naltrexone hydrochloride does not reduce the risk of suicide in these patients (see Section 4.4 Special warnings and precautions for use).

Opioid Dependence

The following adverse reactions have been reported both at baseline and during the naltrexone hydrochloride clinical trials in opioid addiction at an incidence rate of more than 10%:

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

The incidence was less than 10% for:

Loss of appetite, diarrhoea, 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, rhinorrhoea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.

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

Gastrointestinal: excessive gas, haemorrhoids, diarrhoea, ulcer.

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

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

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

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

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

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

Post-Marketing Experience

Data collected from post-marketing use of naltrexone hydrochloride show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a withdrawal syndrome. Events that have been reported include anorexia, asthenia, chest pain, fatigue, headache, hot flushes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhoea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnoea, rash, increased sweating, and vision abnormalities.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone hydrochloride (naltrexone hydrochloride) used in the treatment of opioid dependence. No casual relationship has been demonstrated. In the literature, endogenous opioids have been theorised to contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, or gonadal hormones. The clinical significance of such changes is not fully understood.

Laboratory Tests

With the exception of liver test abnormalities (see Section 4.4 Special warnings and precautions for use), results of laboratory tests, like adverse reaction reports, have not shown consistent patterns of abnormalities that can be attributed to treatment with naltrexone hydrochloride.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

There is limited clinical experience with naltrexone hydrochloride overdosage in humans. In one study, subjects who received 800 mg daily naltrexone hydrochloride for up to one week showed no evidence of toxicity. In the mouse, rat and guinea pig, the oral LD50s were 1,100 ± 96 mg/kg; 1,450 ± 265 mg/kg; and 1,490 ± 102 mg/kg, respectively. In acute toxicity studies in the mouse, rat and dog, cause of death was due to clonic-tonic convulsions and/or

respiratory failure.

Treatment of Overdosage

In view of the lack of actual experience in the treatment of naltrexone hydrochloride overdose, patients should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control centre for the most up-to-date information.

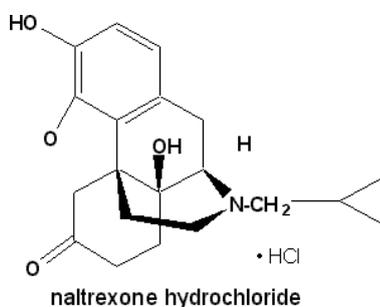
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs; drugs used in addictive disorders, ATC code: N07BB04.

Chemical Structure



Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone hydrochloride is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone. The CAS Registry Number of naltrexone hydrochloride is 16676-29-2. The chemical name of naltrexone hydrochloride is 17-(cyclopropylmethyl)-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride.

Naltrexone hydrochloride is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL.

Mechanism of action

Naltrexone hydrochloride is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of all opioids.

When co-administered with morphine, on a chronic basis, naltrexone hydrochloride blocks the physical dependence to morphine, heroin and other opioids.

Naltrexone hydrochloride has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

Clinical studies indicate that 50mg of naltrexone hydrochloride will block the pharmacologic effects of 25mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of naltrexone hydrochloride provides blockade for 48 hours, and tripling the dose of naltrexone hydrochloride provides blockade for about 72 hours.

Naltrexone hydrochloride blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in

experimental subjects.

The mechanism of action of naltrexone hydrochloride in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone hydrochloride, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone hydrochloride has been shown to reduce alcohol consumption in clinical studies.

Naltrexone hydrochloride is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Tolerance and Dependence

The administration of naltrexone hydrochloride is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, naltrexone hydrochloride will precipitate withdrawal symptomatology.

5.2 Pharmacokinetic properties

Absorption

Naltrexone hydrochloride is a pure opioid receptor antagonist. Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%.

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6- β -naltrexol occur within one hour of dosing. Following the administration of 50 mg tablets to 24 healthy adult male volunteers, the C_{max} values for naltrexone and its major metabolite, 6- β -naltrexol, were 8.6 ng/mL and 99.3 ng/mL respectively

Distribution

Steady state plasma levels of naltrexone and 6- β -naltrexol are achieved rapidly. The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 L. In vitro tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Metabolism

The activity of naltrexone is believed to be due to both parent and the 6- β -naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (55% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and faecal excretion is a minor elimination pathway.

The systemic clearance (after intravenous administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolised) and that extra-hepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6- β -naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6- β -naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

Elimination

The mean elimination half-life (T-1/2) values for naltrexone and 6- β -naltrexol are 4 hours and 13 hours, respectively. The elimination half-life and time to maximum concentration are dose-independent. Naltrexone and 6- β -naltrexol are dose proportional in terms of AUC and C_{max} over the range of 50 to 200 mg and there is no significant accumulation after 100 mg daily doses.

The renal clearance for naltrexone ranges from 30-127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6- β -naltrexol ranges from 230-369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6- β -naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impairment

Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion (see Metabolism above). Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted. In a study, increased bioavailability of naltrexone was observed in patients with liver cirrhosis as compared to healthy subjects. (See Section 4.4 Special warnings and precautions for use: Special Risk Patients).

Clinical Efficacy and Safety

Alcohol Dependence

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

In one of these studies, 104 alcohol-dependent patients were randomised to receive either naltrexone hydrochloride 50mg once daily or placebo. In this study, naltrexone hydrochloride proved superior to placebo in measures of drinking including abstinence rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone hydrochloride were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used. Benefits in preventing relapse were noted in 3 out of 4 trials.

The clinical use of naltrexone hydrochloride as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicentre safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of naltrexone hydrochloride appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with naltrexone hydrochloride reduced alcohol craving, supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies. Naltrexone hydrochloride was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

Opioid Dependence

Naltrexone hydrochloride has been shown to produce complete blockage of the euphoric effects of opioid in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrated an unequivocally beneficial effect of naltrexone

hydrochloride on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative programme, behavioural contract, or other compliance-enhancing protocol.

Naltrexone hydrochloride, unlike methadone, does not reinforce medication compliance and is expected to have a therapeutic effect only when given under conditions that support continued use of the medication.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis

The following statements are based on the results of experiments in mice and rats, which do not form appreciable quantities of the major human metabolite, 6- β -naltrexol.

Thus, the potential carcinogenic, mutagenic and fertility effects of 6- β -naltrexol are unknown.

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males, and tumours of vascular origin in males and females. The incidence of mesotheliomas in males given naltrexone at a dietary dose of 100 mg/kg/day was 6%, compared with a historical incidence of 4%. The incidences of vascular tumours in males and females given dietary doses of 100 mg/kg/day (16 times the recommended therapeutic dose, based on surface area) was 4% but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a 2-year dietary study with naltrexone in male and female mice.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay and in non-specific DNA repair tests with *E. coli*.

However, no evidence of genotoxic potential was observed in a range of other in vitro tests, including assays for gene mutation in bacteria, yeast or in a second mammalian cell line, a chromosomal aberration assay and an assay for DNA damage in cells. Naltrexone did not exhibit clastogenicity in a mouse micronucleus assay.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Naltrexone tablets contain:

Lactose monohydrate
Microcrystalline cellulose
Powdered cellulose
Colloidal anhydrous silica
Magnesium stearate
Crospovidone
Hypromellose
Macrogol 4000
Titanium dioxide
Iron oxide black
Iron oxide red
Iron oxide yellow.

6.2 Incompatibilities

Nil

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

Keep the tablets stored in the original carton until use.

6.5 Nature and contents of container

Naltrexone tablets are supplied in blister packs enclosed in cardboard cartons.

Cartons of 30 tablets are available.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Max Health Ltd

PO Box 65 231

Mairangi Bay

Auckland 0754

Telephone: (09) 815 2664.

9. DATE OF FIRST APPROVAL

01 October 2020

10. DATE OF REVISION OF THE TEXT

01 October 2020

Summary table of changes

Date of Revision	Section Changed	Summary of new information