stearate, microcrystalline cellulose, hydroxypropyl methyl cellulose, polyethylene glycol, polysorbate 80, titanium dioxide, yellow iron oxide and red iron oxide.

Stability and Storage Recommendations
Store at controlled room temperature (15°-30°C). Dispense in a tight container as defined in the USP.

AVAILABILITY OF DOSAGE FORMS

RPC-NALTREXONE (naltrexone hydrochloride) is available as 50 mg, light yellow, capsule-shaped, biconvex, film coated tablets. Debossed with “5” &”0” on either side of score line on one side and "R P" on the other side. Bottles of 30 & 50 and blister pack in cartons of 30, 50 and 100 tablets.

INFORMATION FOR THE CONSUMER

Patient Information Leaflet

PrRPC-NALTREXONE (Naltrexone Hydrochloride) 50 mg Tablets

Please read this leaflet carefully before you start to take RPC-NALTREXONE. If you have any questions or are not sure about anything just ask your doctor or pharmacist.

USE

RPC-NALTREXONE is used together with your other forms of treatment such as counselling to help you to remain free from your dependence on alcohol, heroin, methadone or other similar opiate drugs of addiction.

HOW IT WORKS

Opiate drugs affect certain parts of the brain known as opiate receptors, producing euphoria (or "a high") and other effects. RPC-NALTREXONE is an opiate receptor blocker. RPC-NALTREXONE locks onto these receptor sites and blocks the effects of opiate drugs as well as the body's own opioids. The body's own opioids which occur naturally in the brain may be involved in alcoholism. While it is not completely understood how naltrexone hydrochloride works, in the treatment of alcoholism, in patients who have stopped drinking, naltrexone hydrochloride may help to prevent a return to heavy alcohol use. RPC-NALTREXONE will not make you sick as a result of drinking alcohol. It is not addictive.

HOW TO TAKE IT

For the treatment of alcoholism, the recommended daily dose is 50 mg.
If you are being treated for opioid dependence, you must have stopped taking opiate drugs for at least 7-10 days. Your physician will carry out a test which will show that you are free from these drugs before starting treatment. You will be given a starting dose of 25 mg and then one tablet (50 mg) daily, or it may be more convenient to take two tablets (100 mg) on Monday and Wednesday, and three tablets (150 mg) on Friday. Your doctor will decide which is best for you.

WHAT HAPPENS IF YOU MISS A DOSE

It is important to continue taking RPC-NALTREXONE as it only remains effective against alcohol and opiate drugs as long as you continue to take the tablets.

If you forget one dose it would have no long term consequences as the effect of RPC-NALTREXONE lasts for up to two days, but take the tablet as soon as possible. However, do not double-up on your dose. Do not take more than your prescribed dose.

If you stop taking RPC-NALTREXONE and re-start the use of opiate drugs or alcohol, there is a danger that you will relapse and become dependent on these drugs or alcohol again.

If you have restarted opiate drugs you must not take RPC-NALTREXONE until you have seen your doctor, who will make sure you are opiate free.

If you take RPC-NALTREXONE right after taking an opiate you will suffer withdrawal symptoms (cold turkey) (such as nausea, vomiting, shakiness, sweating and anxiety) which may be severe.

DURATION OF TREATMENT

You should continue to take RPC-NALTREXONE for as long as it is prescribed by your doctor. This could be for three months or longer. RPC-NALTREXONE does not produce "a high" and you cannot become addicted to it.

WHAT HAPPENS IF YOU DRINK ALCOHOL WHILE TAKING RPC-NALTREXONE

You should not experience any unpleasant reaction if you drink alcohol while taking RPC-NALTREXONE. However, your blood alcohol level will still increase and you will become physically and mentally impaired if you do drink alcohol while taking RPC-NALTREXONE.

WARNINGS

Do not take opiates [including methadone or LAAM (levo-alpha-acetyl-methadol)] in an attempt to overcome the blocking effects of RPC-NALTREXONE. If you do, then you could be in trouble. Large doses of opiates can lead to difficulty in breathing and even to death.

Do not give your tablets to other people particularly those who are known to be dependent on opiate drugs because a withdrawal syndrome "cold turkey" may be precipitated. Signs and symptoms (such as nausea, vomiting, shakiness, sweating and anxiety) which may be severe, may develop within five minutes. If this happens call a doctor.

You should not take RPC-NALTREXONE if you are allergic to this product, or if you have acute hepatitis or liver failure. However, your doctor will advise you on these matters when the possibility of RPC-NALTREXONE treatment is first discussed.

Your doctor will request that a blood sample is taken before you start treatment and at various times during treatment. This is necessary because RPC-NALTREXONE is processed by the liver and these tests indicate if your liver is working well.

Do not drink alcohol during the time you are taking RPC-NALTREXONE as this could cause damage to your liver. If you develop abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of your eyes, you should stop taking RPC-NALTREXONE immediately and see your doctor as soon as possible.

Tell your doctor if you are pregnant or breast-feeding as the effects of RPC-NALTREXONE on the baby are not known.

If you experience any unusual sensations or feel unwell after starting RPC-NALTREXONE tell your doctor.

Some medicines may contain opiates, for example certain cough medicines, antidiarrheals (such as kaolin with morphine) and analgesics (pain killers). RPC-NALTREXONE may block the effects of these medicines. If you are ill and require treatment you must tell the doctor or pharmacists that you are taking RPC-NALTREXONE. They can then recommend a medicine which will be effective.

OVERDOSE

In the event of an accidental overdose go to your nearest hospital emergency department or tell your doctor immediately, even though you may not feel sick.

If you think you, or a person you are caring for, have taken too much RPC-NALTREXONE, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

STORING YOUR MEDICINE

Store at controlled room temperature (15°-30°C). Dispense in a tight container.

Keep your tablets in a safe place where children cannot reach them. These tablets could harm them.

If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist.

If you want more information about RPC-NALTREXONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Information For The Consumer by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (https://www.rusanpharma.com/canada/index.html), or by calling 1-450-254-1328.

This leaflet was prepared by Rusan Pharma Canada Inc.

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PHARMACOLOGY

Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone, and differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone (NARCAN* (naloxone hydrochloride injection)), and is, technically, a thebaine derivative. However, it has no opioid agonist properties.

Naltrexone has been shown to be a potent orally effective and safe antagonist of a variety of opioid responses in rodents.

Naltrexone was 16 times more potent than naloxone in preventing etonitazene-induced Straub tail in female mice when administered p.o., but was only 1.6 times as potent when administered s.c.. In male mice, naltrexone was 11 times as potent as naloxone p.o., but was only 1.5 times as potent as naloxone s.c.. The greater relative oral potency suggests that in mice, naltrexone may be better absorbed orally than naloxone. Naltrexone was also shown to be a potent antagonist of:

1. oxycodone-induced Straub tail in mice (p.o.)

2. oxycodone blockade of phenylquinone-induced writhing in mice (p.o.)

3. morphine-induced catalepsy in rats (p.o., s.c.)

4. oxymorphone-induced loss of righting reflex in rats (s.c., i.v.)

Naltrexone competitively inhibited ^{3}H-naloxone and ^{3}H-dihydromorphine binding to the μ-receptor in rat brain membranes, and had a 5 times greater affinity for the μ-receptor than did naloxone.

Naltrexone has no selective anti-writhing activity in the phenylquinone-induced writhing test in mice (p.o., s.c.). The naltrexone antiphenylquinone effects were seen only at doses close to the toxic level, which suggests that they were not due to analgesia. Naltrexone had no analgesic activity in rats, and was virtually inactive in the rat phenylquinone-induced writhing test.

Naltrexone had an anesthetic effect 1.4 times as potent as naloxone and 0.27 times as potent as lidocaine on the sciatic nerve in rats when injected perineurally. In a study on the behavioral and autonomic effects and acute toxicity of naltrexone orally in mice and rats, naltrexone showed a low order of toxicity. Naltrexone caused only ataxia and loss of auditory pinna reflex in mice and no behavioral effect up to and including 324 mg/kg in rats.

Preclinical studies have demonstrated interactions between alcohol and opioid receptor activity. Morphine suppresses alcohol withdrawal in mice and alcohol suppresses morphine withdrawal in rats, indicating pharmacological cross-tolerance. In addition, opioid antagonists (i.e., naltrexone) have been shown to block some of the effects of alcohol, including behavioural symptoms of alcohol withdrawal in mice and rats. Naloxone also blocks alcohol-elicited increases in motor activity in mice.

Preclinical evidence suggests that opiate antagonists can decrease alcohol consumption. For example, rats increase alcohol intake following inescapable but not escapable shock. Injections of

naltrexone were found to block this increase in drinking following inescapable shock, when compared with rats given placebo injections.

Volpicelli (1987) and Volpicelli et al. (1986) studied a model of alcohol drinking in rats based on the observation that alcohol drinking often occurs following uncontrollable events. He referred to human studies supporting the notion that alcohol drinking increases following, but not during arousing situations. Alcohol-drinking rats increased their consumption of alcohol following the receipt of an inescapable electric shock. The large increases in alcohol consumption did not occur on days in which shock was administered but increased on the day after inescapable shock. Naltrexone, 10 mg/kg subcutaneously, blocked post-shock alcohol consumption whereas placebo-treated post-shock rats increased their consumption of alcohol.

The effects of naltrexone and naloxone were studied on the ability to train rats to consume various concentrations of alcohol. Sprague-Dawley rats were treated with either naltrexone or naloxone administered intraperitoneally (i.p.) 15 minutes prior to a 30-minute alcohol drinking access period. Both naltrexone and naloxone dose-dependently decreased the voluntary consumption of a 20% weight/volume solution of alcohol ($p<0.01$).

The effects of naltrexone in decreasing alcohol intake has also been demonstrated in rhesus monkeys. Eight drug-naive rhesus monkeys were trained to self-administer at least 1.0 g/kg/day intravenous alcohol during a 4-hour daily session. Intramuscular administration of either saline or naltrexone (1, 3, or 5 mg/kg) was given 30 minutes before each daily session. Saline pretreatment periods were 10 days in duration and were alternated with 15 days of naltrexone treatment. Naltrexone decreased the self-administration of alcohol in a dose-dependent manner. Altshuler et al. (1980) suggested that the blockade of opioid receptors by naltrexone was responsible for the attenuation of the reinforcing effects of alcohol.

Naltrexone also decreased the consumption of alcohol in another experimental model in rhesus monkeys. Monkeys were trained to drink an alcohol solution under experimental conditions where they had free access to a continuous supply of water and alcohol. The effect of intramuscularly-administered naltrexone was studied (a) during the continuous supply of alcohol, and (b) after a two-day period of imposed abstinence from alcohol. Naltrexone significantly decreased the voluntary consumption of alcohol compared to placebo during both the continuous supply condition and after the two-day abstinence from alcohol. The decrease of drinking was selective since water drinking was not significantly affected by naltrexone.

The pharmacokinetics, tissue distribution and metabolism of naltrexone have been studied in male New Zealand White rabbits. After an intravenous bolus, the plasma half-life of naltrexone between 30 minutes and 3 hours was 55 ± 5 minutes and 53 ± 3 minutes for 1 and 5 mg/kg doses of naltrexone HCl, respectively. The drug concentration in the semen reached a maximum value between 15 and 30 minutes after the injection. At 120 minutes, the semen/plasma drug concentration ratio was 14 and 11 for the 1 and 5 mg/kg doses, respectively. Three minutes after injection 95% of the drug had left the plasma. After 5 minutes the conjugate levels exceeded the free drug levels in the plasma, suggesting rapid glucuronidation of the drug. Ninety minutes after injection, most of the tissues had concentrations of naltrexone and 6-β-naltrexol which exceeded the concurrent plasma concentration. Highest concentrations were observed in the submaxillary gland. Relatively high amounts of 6-β-naltrexol were found in the brain, fat, spleen, heart, testis, kidney and urine. The principal urinary metabolite was the glucuronide of naltrexone with 6-β-naltrexol and N-dealkylated naltrexone as minor metabolites.

The serum kinetics of 5 mg/kg intravenous naltrexone were studied in the dog. Serum samples were obtained from 2 minutes to 2 hours after injection and drug concentrations determined by radioimmunoassay. Serum levels of naltrexone fell rapidly; serum half-life during the elimination phase was 85.1 ± 9.0 minutes (mean ± SE).

Plasma level-time data for intravenous naltrexone at two dose levels in monkeys yielded no evidence of dose-dependent kinetics. A total body clearance of 51-55 mL/min/kg was demonstrated in two dogs. Urine (0-24 hours) contained 36% of the dose as naltrexone conjugates with less than 1% as unchanged naltrexone. Plasma level-time data for intravenous naltrexone in six monkeys yielded an average terminal half-life of 7.8 hours and a total body clearance of 64 mL/min/kg. The total body clearance for naltrexone was greater than the hepatic plasma or blood flow in both dogs and monkeys suggests, together with the extremely low renal excretion of naltrexone, the existence of elimination mechanisms besides liver metabolism and renal excretion.

In rabbits, monkeys and rats, naltrexone is reduced primarily to β-naltrexol. Monkeys receiving a daily oral dose of 12 mg/kg chronically, excreted very little free β-naltrexol and exhibited an apparent sex-related difference in excretion patterns, with females excreting more than twice as much total base as males. Rabbits given an intraperitoneal dose of 30 mg/kg for 4 days excreted conjugated naltrexone as the predominant urinary metabolite, accounting for 80% of total base recovered in 24 hours. In rats receiving 100 mg/kg orally, less than 1% of the administered dose could be accounted for in the 24-hour urine, indicating that although the β-naltrexol is produced as a urinary metabolite, other means of disposition of the drug must exist. Thus, in man and the monkey, β-naltrexol is the predominant and persistent urinary metabolite.

The extent of binding of (15,16-^{3}H)-naltrexone is independent of naltrexone concentration over the concentration range of 1-500 ng/mL for dog plasma and of 0.1 - 500 ng/mL for human, monkey, guinea pig, rat and mouse plasma, ranging from 20% bound in rat plasma to 26% in plasma from beagle and mongrel dogs. This is consistent with previous findings of a large apparent volume of distribution in the dog. Determination of the tissue levels of radioactivity in mice at 1, 5, and 15 minutes after intravenous administration of (8-^{3}H)-naltrexone showed that naltrexone was rapidly distributed from plasma to tissues, with less than 4% of the dose present in plasma at one minute after injection.

The elimination of radioactivity after (15,16-^{3}H)-naltrexone administration i.v. was studied in rats and guinea pigs. An average of 42% of the dose was eliminated in urine and 55% in feces. Radioactivity levels in the excreta of one rat dosed i.m. yielded similar results. Guinea pigs which received 1 mg/kg i.v. excreted only 14% of the dose in feces and 84% in urine. Similar results were obtained following i.m. administration to guinea pigs. In guinea pig excreta, an average of 64% of the dose corresponded to naltrexone and conjugates, 19% to β-naltrexol and conjugates, and 2% to a-naltrexol and conjugates. In urine, the radioactivity corresponding to α-naltrexol and naltrexone was present mainly in conjugated form, whereas apparent β-naltrexol was mainly unconjugated. The radioactivity in feces corresponded principally to unconjugated naltrexone and β-naltrexol.

After subcutaneous injection of (15,16-^{3}H)-naltrexone (10 mg/kg) in male Wistar rats, peak concentrations of drug occurred in brain and plasma within 0.5 hours. Levels of naltrexone were sustained in brain between 2 and 24 hours and were barely detectable at 48 hours. The half-lives of naltrexone in brain and plasma were approximately 8.0 and 11.4 hours, respectively. The brain/plasma ratios of naltrexone at earlier times (0.5-1 hours) were higher than those at later times. The binding of naltrexone in vitro with rat plasma proteins in concentrations of 1-10 µg/mL ranged between 41% and 59%. 6-β-Naltrexol was present in very small amounts in brain but not in plasma. In addition to 7,8-dihydro-14-hydroxynormorphinone and 7,8-dihydro-14

hydroxynormorphine, tentative evidence was obtained for three other metabolites of naltrexone in brain. These metabolites were also present in plasma in addition to free and conjugated naltrexone and its N-dealkylated metabolites.

TOXICOLOGY

Test parameters and drug-related findings of toxicology studies carried out with naltrexone are summarized in the following table:

Acute Toxicity	**Dose (mg / kg)**	**Drug-Related Findings LD_{50} (mg/kg)**			
Species		**p.o.**	**s.c.**	**i.v.**	**i.p.**
Mouse	Various	1100	570	95,180*	332
Rat	Various	1450	1930	117	---
Guinea Pig	Various	1490	301	--	--
Dog	Various	>130	200	117	--

*two tests

In the acute toxicity studies in the mouse, rat, and dog, cause of death was due to clonic-tonic convulsions and/or respiratory failure.

Species	**Duration**	**Dose (mg/kg/day)**	**Observations**
Sub chronic Toxicity Studies			
Rat	90 day	35,70,560 p.o.	No significant findings.
Rat	30 day	3,15,300 S.C.	No significant findings.
Dog	90 day	20,40,100 p.o.	Emesis at 100 mg/kg/d; no other significant findings
Dog	3 week	0.8,4,20 i.v.	Emesis, salivation, urination and other signs; decreased adrenal weights in females.
Dog	28 day	2,10,50 S.C.	Emesis, salivation, mild tremors and muscular weakness at 50 mg/kg/d; no other significant findings.
Chronic Toxicity Studies			
Monkey	1 year	1,5,10,20 p.o.	No significant findings
Carcinogenicity Studies			
Mouse	24 months	30, 100 p.o.	No significant findings
Rat	24 months	30, 100 p.o.	No significant findings

In the two-year carcinogenicity study in rats, there were small increases in the numbers of mesotheliomas in males, and tumours of vascular origin in both sexes. The number of tumours were within the range seen in historical control groups, except for the vascular tumours 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.

Reproduction Studies: Naltrexone hydrochloride has been shown to have embryocidal and fetotoxic effects in rats and rabbits when given in dosages 30 and 60 times, respectively, the human dose.