Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ethylex 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg naltrexone hydrochloride
Contains lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Capsule shaped, beige film-coated tablets with a break-score on each side.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use as an additional therapy within a comprehensive treatment program including psychological guidance for alcohol dependence to support abstinence.

4.2 Posology and method of administration

Ethylex treatment should be initiated and supervised by suitably qualified persons.
Administration of Ethylex should not be started before a naloxone challenge test is performed and a negative result obtained (see section 4.4).
Treatment with Ethylex should be considered only in patients who have remained opioid-free for a minimum of 7-10 days.

Posology

Use in adults
The recommended dose of naltrexone hydrochloride in adults is 50 mg per day (1 tablet).

As Ethylex is an adjunctive therapy and the full recovery process from alcohol dependence is individually variable, no standard duration of treatment can be stated; an initial period of three months should be considered. However, prolonged administration may be necessary.

Use in children and adolescents
Ethylex is not recommended for use in patients below 18 years of age. Safe use in children has not been established.

Use in elderly
There is insufficient data on the safety and efficacy of naltrexone for this indication in elderly patients.

4.3 Contraindications

Ethylex is contraindicated:

- in patients with acute hepatitis or liver failure.
- in patients currently dependent on opioids since an acute withdrawal syndrome may ensue.
- in any patient who has a positive screen for opioids or who has failed the naloxone challenge test (see section 4.4).
- for use in conjunction with an opioid – containing medication
- in combination with methadone (see section 4.5).
- in patients who have demonstrated hypersensitivity to naltrexone hydrochloride or any of the excipients.

- severe renal failure

4.4 Special warnings and precautions for use

In accordance to national guidance the therapy should be initiated and supervised by a physician experienced in treatment of alcohol-addicted patients.

Since Ethylex is extensively metabolised by the liver and excreted predominantly in the urine, caution should be observed in administering the drug to patients with impaired hepatic or renal function. Liver function tests should be carried out both before and during treatment.

Liver function test abnormalities have been reported in obese and elderly patients taking naltrexone who have no history of drug abuse. Liver function tests should be carried out both before and during treatment.

It is not uncommon for opioid abusing individuals to have impaired liver function. In addition, it is not unusual for alcohol abusers to have altered liver function. Changes in hepatic function tests have been described in obese elderly patients receiving naltrexone at doses higher than recommended (up to 300 mg/day) for the treatment of alcoholism. Liver function tests should be performed before starting treatment and periodically throughout treatment.

A withdrawal syndrome may be precipitated by Ethylex in opioid dependent patients; signs and symptoms may develop within 5 minutes and last up to 48 hours. Treatment should be symptomatic and may include opioid administration.

In an emergency situation in which the administration of opioid analgesics is required in patients receiving Ethylex, a higher than usual dose of opioid analgesics may be administered to have the same therapeutic effect. The resulting respiratory depression may be deeper and more prolonged and non-receptor mediated effects may also appear (e.g. swelling of the face, pruritus, generalized erythema, diaphoresis, and other dermal and mucosal symptoms presumably due to histamine liberation). In these circumstances, the patient must be carefully monitored by trained personnel in a hospital center.

During the treatment with Ethylex, painful conditions should be treated with non-opioid analgesia only.

Patients should be warned that attempts to overcome the blockade by administering large doses of opioids may result in acute opioid intoxication after the end of the naltrexone effect which may be possibly life threatening. High dose opioid intake, concomitant with naltrexone treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment.

Patients must be cautioned about the concomitant use of opioids (e.g. opioids in cough preparations, opioids for symptomatic treatment of colds or opioids in antidiarrhoeal preparations etc.) during treatment with naltrexone.

A naloxone provocation is recommended to screen for presence of opioid use; a withdrawal syndrome precipitated by naloxone will be of shorter duration than a withdrawal precipitated by Ethylex.

The naloxone-challenge test should neither be performed in patients with clinically significant withdrawal symptoms nor in patients tested positive for opioids in the urine.

The recommended procedure is as follows:

Intravenous provocation

- Intravenous injection of 0.2 mg naloxone
- If after 30 seconds no adverse reactions occur, a further i.v. injection of 0.6 mg naloxone may be administered
- The patient should be continuously observed for 30 minutes to exclude any detectable sign of withdrawal symptoms.

If any symptoms of withdrawal occur naltrexone-therapy must not be undertaken. If the test-result is negative the treatment can be initiated. If any doubt exists that the patient is opioid-free, the challenge may be repeated with the dosage of 1.6 mg. If no reaction occurs after this, 25 mg of naltrexone hydrochloride can be administered to the patient.

Naltrexone treatment must begin only when the opioid has been discontinued for a sufficiently long period (about 5 to 7 days for heroin and at least 10 days for methadone).

The risk of suicide is known to increase in substance abusers, with or without concomitant depression. Treatment with INVENTED NAME does not eliminate this risk.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Presently, clinical experience and experimental data on the effect of naltrexone on the pharmacokinetics of other substances are limited. Concomitant treatment with naltrexone and other medicinal products should be conducted with caution and should be followed carefully.
No interaction studies have been performed.

In vitro studies have shown that neither naltrexone nor its active metabolite 6-beta-naltrexol is metabolised by human cytochrom P450 enzymes. Therefore it is unlikely that the pharmacokinetics of naltrexone hydrochloride is affected by cytochrom P450 enzyme inhibiting drugs.

Association contraindicated: opioid derivates (analgesics, antitussives, substitution treatments). Concomitant administration of naltrexone with an opioid-containing medication is contraindicated.
Methadone in substitution treatment: There is a risk of onset of withdrawal syndrome.

Association not recommended: central antihypertensives (alpha-methyldopa).

Association to be taken into account: barbiturates; benzodiazepines; anxiolytics others than benzodiazepines (i.e. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, trimipramine), sedative antihistaminics H1, neuroleptics (droperidol).

Until now no interaction between cocaine and naltrexone hydrochloride has been described.

Data from a safety and tolerability study of co-administration of naltrexone with acamprosate in non-treatment seeking, alcohol dependent individuals showed that naltrexone administration significantly increased acamprosate plasma level. Interactions with other psychopharmacological agents (e.g. disulfirame, amitryptiline, doxepine, lithium, clozapine, benzodiazepines) have not been investigated.

There are no known interactions between naltrexone and alcohol.

There have been reports of cases of lethargy and somnolence following concomitant administration of naltrexone and thioridazine.

Concomitant use with opioid containing medicines is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no clinical data on naltrexone hydrochloride use in pregnancy. Data from animal studies have shown reproductive toxicity (see section 5.3). The data are insufficient to establish clinical relevance. The potential risk for humans is unknown. Naltrexone should only be given to pregnant women when, in the judgment of the attending physician, the potential benefits outweigh the possible risk.

The use of naltrexone in pregnant alcoholic patients receiving long-term treatment with opiates or substitution treatment with opiates, or in pregnant patients who are opioid dependent, creates a risk of acute withdrawal syndrome which could have serious consequences for the mother and the foetus (see section 4.4). Naltrexone administration must be suspended if opiate analgesics are prescribed (see section 4.5).

Lactation:
There are no clinical data on naltrexone hydrochloride use in lactation. It is unknown whether naltrexone or 6-beta-naltrexol is excreted in human breast milk. Breast feeding is not recommended during naltrexone treatment.

4.7 Effects on ability to drive and use machines

Ethylex 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

The following adverse reactions have been reported before and during naltrexone medication:
Frequency is defined using the following convention:

Very common (≥ 1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1.000 to < 1/100)
Rare (≥ 1/10.000 to < 1/1.000)
Very rare (< 1/10.000)

The side effects observed with naltrexone appear to be similar in both alcoholics and patients dependent on opioids. Serious adverse reactions are unusual.

Blood and lymphatic system disorders
Uncommon: lymphadenopathy
Rare: idiopathic thrombocytopenic purpura

Psychiatric disorders
Very common: nervousness, anxiety, insomnia
Common: irritability, affective disorders
Uncommon: hallucination, confusional state, depression, paranoia, disorientation, nightmare, agitation, libido disorder, abnormal dreams
Rare: suicidal ideation, attempted suicide

Nervous system disorders
Very common: headache, restlessness
Common: dizziness
Uncommon: tremor, somnolence

Eye disorders
Common: lacrimation increased
Uncommon: vision-blurred, eye irritation, photophobia, eye swelling, eye pain or asthenopia

Cardiac disorders
Common: tachycardia, palpitations, electrocardiogram change

Vascular disorders
Uncommon: blood pressure fluctuation, flushing
Respiratory disorders
Common: chest pain
Uncommon: nasal congestion, nasal discomfort, rhinorrhea, sneezing, oropharyngeal pain, sputum increased, sinus disorder, dyspnoea, dysphonia, cough, yawning

Gastrointestinal disorders
Very common: abdominal pain, nausea and/ or vomiting
Common: diarrhoea, constipation
Uncommon: flatulence, haemorrhoids, ulcer, dry mouth

Hepatobiliary disorders
Uncommon: liver disorder, blood bilirubin increased, hepatitis (During treatment an increase of liver transaminases may occur. After discontinuation of Ethylex the transaminases decreased to baseline within several weeks.)

Skin and subcutaneous tissue disorders
Common: rash
Uncommon: seborrhoea, pruritus, acne, alopecia

Musculoskeletal and connective tissue disorders
Very common: arthralgia and myalgia
Uncommon: groin pain
Very rare: rhabdomyolysis

Reproductive system and breast disorders
Common: ejaculation delayed, erectile dysfunction

Renal and urinary tract disorders
Uncommon: pollakiuria, dysuria

Ear and labyrinth disorders
Uncommon: ear discomfort, ear pain, tinnitus, vertigo

Infections and infestations
Uncommon: oral herpes, tinea pedis

Metabolism and nutrition disorders
Common: decreased appetite

General disorders
Very common: asthenia
Common: thirst, energy increased, chills, hyperhidrosis
Uncommon: increased appetite, weight loss, weight gain, pyrexia, pain, peripheral coldness, feeling hot

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

There is limited clinical experience with Ethylex overdose in patients. There was no evidence of toxicity in volunteers receiving 800 mg/day for seven days, however, in case of overdose, patients should be monitored and treated symptomatically in a closely supervised environment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in alcohol dependence
ATC code: N07B B04

Naltrexone is a specific opioid antagonist with only minimal agonistic activity. It acts by stereospecific competition with receptors which are mainly located in the central and peripheral nervous system. Naltrexone competitively binds to these receptors and blocks the access for exogenously administered opioids.

Naltrexone treatment does not lead to physical or mental dependence. No tolerance for the opioid antagonising effect is seen.

The mechanism of action of naltrexone in alcoholism is not completely elucidated, however an interaction with the endogenous opioid system is suspected to play an important role. Alcohol consumption in humans has been hypothesised to be reinforcing through an alcohol-induced stimulation of the endogenous opioid system.

Naltrexone is not an aversive therapy and does not cause a disulfiram-like negative reaction when alcohol is ingested.

The prominent effect of naltrexone treatment of alcohol-addicted patients seems to be a reduction of the risk of a full relapse with uncontrolled binge-drinking after having consumed a limited amount of alcohol. This gives the patient a "second chance" to escape the otherwise mutually reinforcing mechanisms of a full relapse with complete loss of control. Naltrexone also seems to have an effect on the primary craving as it is non-reinforcing on isolated consumption of limited amounts of alcohol.

5.2 Pharmacokinetic properties

Naltrexone is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration.
It undergoes a liver first-pass effect and peak plasma concentration is reached within approximately one hour.
Naltrexone is hydroxylated in the liver basically to the main active metabolite 6-beta-naltrexol and, to a lesser extent, to 2-hydroxy-3-methoxy-6-beta-naltrexol.

The plasma-half-life of naltrexone is approximately 4 hours, the average blood level is 8,55 ng/ml, and plasmaprotein-binding is 21%. The plasma-half-life of 6-beta-naltrexol is 13 hours.

The medicinal product is excreted primarily renally. About 60% of the peroral dose is excreted within 48 hours as glucuronidised 6-beta-naltrexol and naltrexone.

Five to ten times higher plasma concentrations of naltrexone have been reported in cirrhotic patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. However, there is some evidence on hepatotoxicity with increasing dose, since reversible increases of liver enzymes have been found in humans with therapeutic and higher doses (see section 4.4 and 4.8).

Naltrexone (100 mg/kg, approximately 140 times the human therapeutic dose) caused a significant increase of pseudo-pregnancy in rats. A decrease of the pregnancy rate of mated female rats also occurred. The relevance of these observations to human fertility is not known.

Naltrexone 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 100 mg/kg of naltrexone prior to and throughout gestation, and rabbits treated with 60 mg/kg of naltrexone during the period of organogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Powered cellulose
Microcrystalline cellulose
Silica, colloidal anhydrous
Crospovidone
Magnesium stearate

Film-coat: Opadry 31 F 27245 Beige
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Black ferric oxide (E172)

Red ferric oxide (E172)
Yellow ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Pack sizes: 7, 14, 28, 30 and 56 tablets in PVC/PVDC/Aluminium blister

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Walter Ritter GmbH & Co. KG
Spaldingstrasse 110 B
Klostertor
Hamburg
20097
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8 MARKETING AUTHORISATION NUMBER

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