SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adepend 50 mg filmcoated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg naltrexone hydrochloride.
Excipients with known effect: contains 126,755 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
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

Adepend is used as part of a comprehensive programme of treatment against alcoholism to reduce the risk of relapse, as support treatment in abstinence and to reduce the craving for alcohol.

4.2 Posology and method of administration

Before treatment, it has to be assured that the patient is free of opioids (see section 4.4).

Treatment with naltrexone should according to national guidelines only be initiated and monitored by physicians experienced with the treatment of alcohol-addicted patients.

Treatment with naltrexone should only be considered for patients who have been for a sufficiently long period free of opioids (see section 4.4).

The treatment should be initiated with low doses of naltrexone according to the treatment induction schedule.

Higher doses than 150 mg even for only one day may result in an increase in side effects and are therefore not recommended.

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

Use in children and adolescents (<18 years)
Adepend 50 mg film-coated tablets are not recommended for use in children and adolsecents below 18 in this indication due to a lack of data on safety and efficacy.

Use in elderly
Safe use for the treatment of opiate dependence in the elderly has not been established.

Use in patients with liver and/or kidney diseases
Adepend 50 mg film-coated tablets are contraindicated for patients with severe liver and/or kidney diseases.

In patients with slight or moderate disorder of liver and/or kidney Adepend 50 mg film-coated tablets should be applied only with special caution and close-meshed supervision (see section 4.4). A dose adaptation should be considered (see section 5.2).

Method of administration
Adepend 50 mg film-coated tablets should be taken with a liquid.

Duration of administration
A common duration of administration cannot be specified as Adepend 50 mg film-coated tablets are used as concomitant therapy and recovery is individually different for patients addicted to alcohol, even if they are psychologically attended. A treatment duration of at least 3 months is recommended whereas a prolongation might be necessary. Efficacy is proven by controlled studies over a period up to 12 months.

Naltrexone hydrochloride neither causes psychical nor physic addiction. There is no decrease of antagonistic effects during long term treatments.

4.3 Contraindications

- Hypersensitivity to naltrexone hydrochloride or to any of the excipients listed in section 6.1
- Acute hepatitis or liver failure
- Severe or acute liver impairment
- Severe renal impairment
- Patients taking opioid-analgesics
- Combination with an opioid-containing medication (see sections 4.4 and 4.5)
- Combination with methadone (see section 4.5)
- Opioid-addicted patients as acute opioid withdrawal symptoms may occur
- Patients with withdrawal symptoms after administering naloxon hydrochloride (positive result of the naloxone provocation test)
- Positive urine test for opioids

4.4 Special warnings and precautions for use

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

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

In opioid-dependent patients, withdrawal symptoms may be caused by Adepend 50

mg film-coated tablets. These may manifest after 5 minutes and least up to 48 hours. The treatment should be symptomatic and may include administration of opioids.

Liver function test

Due to its hepatotoxic effect, special caution should be taken with the administration of Adepend in patients with acute liver disease or liver impairment.

Naltrexone hydrochloride is metabolised mainly by the liver and mainly eliminated by urine. Therefore patients with liver or renal impairment should be supervised carefully during treatment (see section 4.3). Liver function tests should be conducted before and during therapy.

It is not uncommon that the liver function of alcohol addicts is impaired. In elderly, obese alcohol addicted patients, liver function tests have demonstrated abnormal results after administration of higher doses of naltrexone (up to 300 mg/day).

Liver function tests should be carried out both before and during treatment.

Screen for presence of opioid use

In case of the suspicion of opioid dependence it is recommended to screen for the presence of opioid use:

- Urine test: If the suspicion of opioid use is aroused despite a negative urine test result and the lack of visible clinical withdrawal symptoms, it is recommended to confirm the result of the urine test with a naloxone challenge test.
- Naloxone challenge test: Withdrawal symptoms caused by naloxone hydrochloride are of shorter duration than those precipitated by Adepend 50 mg film-coated tablets.

  A naloxone challenge test should neither be performed in patients with clinically significant withdrawal symptoms nor in patients tested positive for opioids in the urine. If withdrawal symptoms should occur during this test the treatment with Adepend 50 mg film-coated tablets must not be initiated. The treatment may be initiated following a negative test result.

  Recommended administration scheme:

- Intravenous: Administer 0.2 mg naloxone iv. If no adverse reactions appear after 30 seconds, administer another dose of 0.6 mg naloxone iv. Continue observing the patient over 30 minutes for signs of withdrawal.
- Subcutaneous: Administer 0.8 mg naloxone sc. Observe the patient for 30 minutes for signs of withdrawal.

  Confirmation of the test: If there is any doubt that the patient is opioid-free, treatment with Adepend 50 mg film-coated tablets should be delayed 24 hours. In this case, the test should be repeated with 1.6 mg naloxone.

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

Patients must be warned against the use of high doses of opioids to neutralize the blockade as this might result in acute and possibly fatal opioid intoxication as soon as the effect of naltrexone has ceased. High-dose opioid intake, concomitant with naltrexone treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment.

Patients might be more sensitive to opioid containing medicines after treatment with Adepend 50 mg film-coated tablets.

Naltrexone may cause a transient increase in the diastolic blood pressure followed by decrease in body temperature and heart rate.

Patients must be warned against concomitant use of opioids (e.g. opioid containing cough medication, opioid containing medication for symptomatic treatment of common cold or opioid containing medication for diarrhea etc.) during treatment with Adepend 50 mg film-coated tablets.
If the patient treated with Adepend 50 mg film-coated tablets needs opioid treatment, e.g. opioid analgesia or anesthesia in emergency situations, the dose needed may be higher than normal to reach the same therapeutic effect. In these cases, respiratory depression and circulatory disturbance will be more profound and longer lasting. Symptoms related to release of histamine (e.g. face swelling, itching, erythema, diaphoresis and other skin and mucocutaneous manifestations) can occur more easily. The patient requires specific attention and supervision by health care personnel in a medical unit.

The increased suicidal risk in drug addicts with or without accompanying depression is not reduced by the intake of Adepend 50 mg film-coated tablets.

Special attention should be paid to patients with hepatic enzyme levels in serum exceeding three times the normal value and patients with renal impairment.

Lactose: Patients with the rare hereditary 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

At the moment, there is only limited clinical experience and experimental data on the effect of naltrexone on the pharmacokinetics of other substances. Concomitant treatment with naltrexone and other medicinal products should be conducted with caution and should be followed carefully. No studies for interactions have been performed.

Cases of lethargy and somnolence have been reported after concomitant use of naltrexone and thioridazine.

In vitro studies have shown that neither naltrexone hydrochloride nor its active metabolite 6-beta-naltrexol is metabolised by human cytochrom P450 enzymes. Therefore it is unlikely that the pharmacokinetics of Adepend 50 mg film-coated tablets is affected by cytochrom P450 enzyme inhibiting or inducing drugs:

Patients might be more sensitive to opioid containing medicines after treatment with Adepend 50 mg film-coated tablets.

Contraindicated combinations: Concomitant use of naltrexone with opioid derivates (analgesics, antitussives, substitution treatments) is contraindicated (see section 4.3 and 4.4).
Methadone in substitution treatment: There is a risk of onset of withdrawal symptoms.

Combinations not recommended: Concomitant use of naltrexone with central antihypertensives (alpha-methyldopa) is not recommended.

Combinations where caution is advised: Concomitant use of naltrexone with barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (e.g. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, trimipramine), sedative antihistamines H1 and neuroleptics (droperidol) may be considered with caution.

So far, 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 the acamprosate plasma level. Interaction with other psychopharmacological agents (e.g. disulfirame, amitryptiline, doxepine, lithium, clozapine, benzodiazepines) has not been investigated.

Currently, interactions between naltrexone and alcohol are not known.

For interactions with opioid containing drugs, please see 4.4.

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 judgement 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 fetus (see section 4.4). Naltrexone administration must be suspended if opiate analgesics are prescribed (see section 4.5).

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

4.7 Effects on ability to drive and use machines

Adepend 50 mg film-coated tablets may influence psychological and physical abilities and, therefore, conduction of potentially dangerous tasks like driving vehicles or using machines should be avoided.

4.8 Undesirable effects

The following undesirable effects are classified according to system organ class and frequency:

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)
Not known (cannot be estimated from the known data)

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

Infections and infestations
Uncommon: oral herpes, tinea pedis

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

Metabolism and nutrition disorders
Common: decrease of appetite

Psychiatric disorders
Very common: nervousness, anxiety, insomnia
Common: irritability, affective disorder
Uncommon: hallucination, confusion, despondency, depression, paranoia, disorientation, nightmares, 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: increased lacrimation
Uncommon: blurred vision, irritation and swelling of the eye, photophobia, eye pain or tiredness, colour asthenopia

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

Cardiac disorders
Common: tachycardia, heart palpitation, anomalies in the ECG

Vascular disorders
Uncommon: blood pressure changes, flushing

Respiratory, thoracic and mediastinal disorders
Common: pain in the chest
Uncommon: nasal congestion, nasal discomfort, rhinorrhoea, sneezing, oropharyngeal disorders, increased sputum, sinus disorders, dyspnoea, dysphonia, coughing, yawning

Gastrointestinal disorders
Very common: abdominal pain, nausea, emesis
Common: diarrhoea, constipation

Uncommon: flatulence, haemorrhoids, ulcus, mouth dryness

Hepatobiliary disorders
Uncommon: hepatic disorders, increased bilirubin levels, hepatitis (During treatment, increase of transaminases is possible. After discontinuing the intake of Adepend, transaminases decrease to the original levels within some weeks.)

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

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

Renal and urinary disorders
Uncommon: pollakisuria, dysuria

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

General disorders and administration site conditions
Very common: asthenia
Common: thirst, increased energy, chills, hyperhidrosis
Uncommon: increased appetite, weight loss, weight gain, fever, pain, sensation of cold in extremities, hot flushes

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

There is limited experience with overdose of naltrexone hydrochloride. There was no evidence of toxicity in volunteers receiving 800 mg naltrexone hydrochloride per day for one week.

Treatment

In case of overdose, patients should be closely monitored and treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in alcohol dependence

ATC code: N07BB04

Naltrexone hydrochloride is an orally used, long acting specific opioid antagonist. Naltrexone hydrochloride binds competitively to receptors which are located in the central and peripheral nervous system and hence blocks the access for exogenously administered opioids.

Treatment with Adepend 50 mg filmcoated tablets does not lead to physical or psychological dependence. No tolerance for the opioid antagonising effect is seen.

The mechanism of action of naltrexone hydrochloride is not completely elucidated. An interaction with the endogenous opioid system is assumed. Alcohol consumption in humans has been hypothesised to reinforce an alcohol-induced stimulation of the endogenous opioid system.

A therapy with Adepend 50 mg filmcoated tablets is a non-aversive therapy and does not cause reactions when alcohol is ingested. Therefore there are also no disulfiram-like reactions.

The main effect of the treatment with Adepend 50 mg filmcoated tablets seems to be a reduction of the risk of a full relapse after having consumed a limited amount of alcohol. This gives the patient the possibility to escape a full relapse with complete loss of control because of decreased stimulation.

Naltrexone hydrochloride reduces the desire for alcohol ("craving") during abstinence and after alcohol ingestion. The reduction of desire for alcohol lowers the risk of a full relapse of abstinent and non-abstinent patients.

5.2 Pharmacokinetic properties

Absorption
After oral administration naltrexone hydrochloride is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentration is reached within one hour.

Distribution
Plasmaprotein-binding is 21%. The steady-state plasma-level is 8.55 mg/ml.

Metabolism
Metabolism takes place mainly by a first-pass effect in the liver. Naltrexone hydrochloride is basically hydroxylated to the main active metabolite 6-beta-naltrexol and, to a lesser extent, to 2-hydroxy-3-methoxy-6-beta-naltrexol.

Elimination
The substance is excreted primarily renally. About 60 % of the perorally given dose is excreted within 48 hours as glucuronidised 6-beta-naltrexol and naltrexone hydrochloride.The plasma-half-life of naltrexone hydrochloride is approximately 4 hours. The plasma-half-life of 6-beta-naltrexol is 13 hours.

Five to ten times higher plasma concentrations of naltrexone hydrochloride 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 and carcinogenic potential. However, there is some evidence on hepatotoxicity with increasing dose. Reversible increases of liver enzymes have been found in patients treated with therapeutic or higher doses (see section 4.4 and 4.8).

Naltrexone hydrochloride (100 mg/kg/day, 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 hydrochloride has been shown to have an embryotoxic effect in 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/day naltrexone hydrochloride prior to and throughout gestation, and rabbits treated with 60 mg/kg/day naltrexone hydrochloride during the period of organogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Powered cellulose

Crospovidone

Microcrystalline cellulose

Silica, colloidal anhydrous

Magnesium stearate

Film-coat:

Lactose monohydrate

Hypromellose

Titanium dioxide (E 171)

Macrogol 4000

Black ferric oxide (E 172)

Red ferric oxide (E 172)

Yellow ferric oxide (E 172)

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 light.

6.5 Nature and contents of container

7, 10, 14, 28, 30 or 100 tablets in PVC/PVDC/Aluminium blister packed in a carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Orpha-Devel Handels und Vertriebs GmbH
Wintergasse 85/1B
A-3002 Purkersdorf
Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 30414/0013

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07/11/2019