Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naltrexone Hydrochloride 50mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50.00 mg naltrexone hydrochloride

Excipient(s) with known effect: Each film-coated tablet contains 192.85 mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Yellow colored, oval, biconvex, film coated tablets with breakline on one side and plain on other 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 detoxified patients who have been opioid-dependent (see section 4.2 and 4.4) & alcohol dependence to support abstinence.

4.2 Posology and method of administration

Use in adults
Naltrexone treatment should be initiated and supervised by suitable qualified physicians.

The initial dose of naltrexone hydrochloride should be 25 mg (half a tablet) for opioid-dependent patient followed by the usual dose of one tablet per day (= 50 mg naltrexone hydrochloride)

A missed dose can be managed by providing 1 tablet per day each day till the next regular dosage-administration.

Naltrexone administered to opioid-dependent persons can cause life-threatening withdrawal symptoms. Patients suspected of using or being addicted to opioids must undergo a naloxone provocation test (see section 4.4), unless it can be verified that the patient has not taken any opioids for 7-10 days (urine test) prior to the initiation of treatment with naltrexone.

As Naltrexone is an adjunctive therapy and the full recovery process in opioid-dependent patients 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.

The recommended dose for alcohol dependence to support abstinence is 50 mg per day (1 tablet). A dose of over 150 mg on any single day is not recommended, since this can lead to a higher incidence of side effects.

As naltrexone hydrochloride 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

The dosage-regimen can be modified in order to improve compliance to a three-times-a-week dosing schedule as follows: administration of 2 tablets (=100 mg naltrexone hydrochloride) on Monday and on Wednesday and 3 tablets (=150 mg naltrexone hydrochloride) on Friday.

Paediatric population

Naltrexone should not be used in children and adolescents under 18 years of age, since clinical data in this age-group are lacking. Safe use in children has not been established.

Older people
There are insufficient data on the safety and efficacy of naltrexone for this indication in elderly patients.

4.3 Contraindications

- Hypersensitivity to naltrexone hydrochloride or to any of the excipients listed in section 6.1.
- Severe renal impairment
- Severe hepatic impairment
- Acute hepatitis
- Opioid addicted patients with a current abuse of opioids since an acute withdrawal syndrome may ensue.
- Positive screening result for opioids or after failure of the naloxone provocation test.
- For use in conjunction with an opioid - containing medication
- In combination with methadone (see section 4.5).

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 opioid-addicted and alcohol-addicted patients

High dose opioid intake, concomitant with Naltrexone treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment.
Should naltrexone be used in opioid-dependent patients a withdrawal syndrome may occur rapidly: the first symptoms can occur within 5 minutes, the last after 48 hours. The treatment of withdrawal symptoms is symptomatic.

It is not uncommon for alcohol abusing individuals to show signs of impaired hepatic function. Abnormal hepatic function test parameters have been reported in obese and elderly patients receiving naltrexone in dosages higher than recommended (up to 300 mg/day). Hepatic function controls should be made before and during treatment. Special attention should be paid to patients with hepatic enzyme levels in serum exceeding three times the normal value and patients with renal impairment.

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.

Patients must be warned against the concomitant use of opioids (e.g. opioids in cough medication, opioids in symptomatic medication for the treatment of common colds, or opioids contained in anti diarrhoeal agents, etc.) during naltrexone treatment (see section 4.3).

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).

If the patient needs opioid treatment, e.g. opioid analgesia or anesthesia in emergency situations, the dose needed may be higher than normal. In these cases, the respiratory depression and circulatory effects will be more profound and longer lasting. Symptoms related to release of histamine (generalized erythema, diaphoresis, itching and other skin and mucocutaneous manifestations) can also be manifested more easily. The patient requires specific attention and care in these situations.

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

Patients should be warned that large doses of opioids to overcome the blockade may after the cessation of the naltrexone result in an acute opioid overdose, with possible fatal outcome.

Patients might be more sensitive to opioid containing medicines after treatment with naltrexone.

Patients suspected of using or being addicted to opioids must undergo a naloxone provocation test, unless it can be verified that the patient has not taken any opioids for 7-10 days (urine test) prior to the initiation of treatment with naltrexone.
A withdrawal syndrome precipitated by naloxone will be of shorter duration than withdrawal precipitated by naltrexone.

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 observed continuously for 30 minutes for 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.
A naloxone hydrochloride provocation test should not be made in patients with clinically prominent withdrawal symptoms nor in any case of a positive urine test for opioids.

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

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

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

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant administration of naltrexone with an opioid-containing medication should be avoided.

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 main metabolite 6-ß-naltrexol is metabolised via human CYP450 enzymes. Therefore it is unlikely that the pharmacokinetics of naltrexone is affected by cytochrome P450 enzyme inhibiting drugs.

Association not recommended: opioid derivatives (analgesics, antitussives, substitution treatments), Central antihypertensives, (alpha-methyldopa).

Concomitant administration of naltrexone with an opioid-containing medication should be avoided.

Methadone in substitution treatment. There is a risk of onset of withdrawal syndrome.

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).

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. Interaction with other psychopharmacological agents (e.g. disulfirame, amitryptiline, doxepine, lithium, clozapine, benzodiazepines) have not been investigated

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

There are no known interactions between naltrexone and alcohol.

For interactions with opioid containing drugs please see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregancy
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 and 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 HCl use in lactation. It is unknown whether naltrexone or 6-beta-naltrexol is excreted in human breast milk. During treatment breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Naltrexone 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 undesirable effects are ranked according to system organ class and to their 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 available data)

MedDRA system organ class	
Infections and infestation	
Uncommon	Oral herpes
	Tinea pedis
Blood and lymphatic system disorders	
Uncommon	Lymphadenopathy
Rare	Idiopathic thrombocytopenic purpura
Metabolism and nutrition disorders	
Common	Decreased appetite
Psychiatric disorders:	
Very common	Nervousness
	Anxiety
	Insomnia
Common	Affective disorders
	Despondency
	Irritability
	Mood swings
Uncommon	Hallucination
	Confusional state
	Depression
	Paranoia
	Disorientation

	Nightmare
	Agitation
	Libido disorder
	Abnormal dreams
Rare	Suicidal ideation
	Attempted suicide
Very rare	Euphoria
Nervous system disorder	
Very common	Headache
	Sleep disorders
	Restlessness
Common	Dizziness
	Shivering
	Vertigo
Uncommon	Tremor
	Somnolence
Rare	Speech disorder
Eye disorders	
Common	Lacrimation increased
Uncommon	Vision-blurred Eye irritation
	Photophobia
	Eye swelling
	Eye pain
	Asthenopia
Ear and labyrinth disorders	
Uncommon	Ear discomfort
	Ear pain
	Tinnitus
	Vertigo
Cardiac disorders	
Common	Tachycardia
	Palpitations
	Electrocardiogram change
Vascular disorders	
Uncommon	Blood pressure fluctuation
	Flushing
Respiratory, thoracic and mediastinal disorder	
Common	Chest pain
Uncommon	Nasal congestion
	Nasal discomfort
	Rhinorrhea
	Sneezing
	Oropharyngeal pain
	Sputum increased
	sinus disorder
	Dyspnoea
	Dysphonia
	Cough
	Yawning
Gastrointestinal disorder	
Very common	Abdominal pain
	Abdominal cramps
	Nausea or Inclination to vomit
	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 Naltrexone the transaminases decreased to baseline within several weeks.
Skin and subcutaneous tissue disorder	
Common	Rash
Uncommon	Seborrhoea
	Pruritus
	Acne
	Alopecia
Very rare	Exanthema

Musculoskeletal and connective tissue disorders:	
Very common	Arthralgia
	Myalgia
Uncommon	Groin pain
Very Rare	Rhabdomyolysis
Renal and urinary disorders	
Common	Urine retention
Uncommon	Pollakiuria
	Dysuria

Reproductive system and breast disorders	
Common	Delayed ejaculation
	Erectile dysfunction
General disorder and administration site conditions	
Very common	Feebleness
	Asthenia
Common	Lack of appetite
	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 the online reporting option (preferred method) accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms

- There is limited clinical experience with naltrexone overdose in patients.
- There was no evidence of toxicity in volunteers receiving 800 mg/day for seven days.

Treatment

- 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: other nervous system drugs; drugs used in addictive disorders
ATC code: N07BB04

- 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.
- Naltrexone Hydrochloride 50 mg film-coated tablets reduces the risk of relapse and supports abstinence from opioids.
- Naltrexone Hydrochloride 50 mg film-coated tablets is a non-aversive therapy and does not cause reactions after opioid intake. Therefore it does not cause a disulfiram-type reaction.
- 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

Absorption
Naltrexone is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration.

Biotransformation
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 mg/ml, and plasmaprotein-binding is 21%. The plasma-half-life of 6-beta-naltrexol is 13 hours.

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

5.3 Preclinical safety data

Preclinical data revealed 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, since reversible increases of liver enzymes has 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 in pseudo-pregnancy in the rat. A decrease in 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
Cellulose Microcrystalline
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Film Coating:
Hypromellose (E464)
Macrogol 400
Polysorbate 80 (E 433)
Iron Oxide Yellow (E172)
Iron oxide red (E172)
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Naltrexone Hydrochloride 50 mg film-coated tablets are packed in White opaque PVC/PE/Aclar – Alu Blister and Alu-Alu blister packs containing 7, 14, 28, 30, 50 and 56 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island

Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/111/001.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2010
Date of last renewal: 31st May 2013

10 DATE OF REVISION OF THE TEXT

May 2019