Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naltrexone 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg naltrexone hydrochloride.
One film-coated tablet contains 126.8 mg lactose monohydrate.

For the 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 detoxified patients who have been opioid-dependent. (see 4.2 and 4.4)

4.2 Posology and method of administration

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

Use in adults

The recommended initial dose of naltrexone hydrochloride is 25 mg (half a tablet) followed by 50 mg per day (one tablet).

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.
A missed dose can be managed by providing 1 tablet per 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 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.

Use in children and adolescents

Naltrexone is not recommended for use in children and adolescents below 18 due to a lack of data on safety and efficacy.

Use in elderly

The experience in elderly patients is limited.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute hepatitis
- Severe hepatic impairment
- Severe renal impairment
- 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.

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 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.

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).

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

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

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.

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.

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.

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 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 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.

One case of lethargy and somnolence has been reported after concomitant use of naltrexone and thioridazine.

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 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 and the possible risk.

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. During treatment breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Naltrexone has minor or moderate influence on the ability to drive and use machines.

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)

MedDRA system organ class	Symptom
Nervous system disorder	
Very common	Headache
	Sleep disorders
	Restlessness
	Nervousness
Common	Thirst
	Dizziness
	Shivering
	Increased transpiration
	Vertigo
Rare	Speech disorder
Very rare	Tremor
Gastrointestinal disorder	
Very common	Abdominal pain
	Abdominal cramps
	Nausea
	Inclination to vomit
Common	Diarrhoea
	Constipation
Hepatobiliary disorders	
Rare	Hepatic disorders
Musculoskeletal and connective tissue disorders	
Very common	Joint and muscle pain
General disorder and administration site conditions	
Very common	Feebleness
Common	Lack of appetite
Eye disorders	
Common	Increased lacrimation
Respiratory, thoracic and mediastinal disorder	
Common	Pain in the chest
Renal and urinary disorders	
Common	Urine retention
Skin and subcutaneous tissue disorder	
Common	Rash
Very rare	Exanthema
Reproductive system and breast disorders	
Common	Delayed ejaculation
	Decreased potency
Psychiatric disorders	
Common	Anxiety
	Increased energy
	Despondency
	Irritability
	Mood swings
Rare	Depression
	Suicidal ideation

	Attempted suicide
Very rare	Agitation
	Euphoria
	Hallucination
Blood and lymphatic system disorders	
Very rare	Idiopathic thrombocytopenic purpurea

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, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie. E-mail: medsafety@hpra.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: Drugs used in alcohol dependence
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 50 mg film-coated tablet reduces the risk of relapse and supports abstinence from opioids.

Naltrexone 50 mg film-coated tablet is a non-aversive therapy and does not cause reactions after opioid intake. Therefore it does not cause a disulfiram-type reaction.

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 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 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 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
Powdered cellulose
Microcrystalline cellulose
Silica, colloidal anhydrous
Crosprovidone
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 size: 7, 14, 28, 30 and 56 tablets in PCV/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

AOP Orphan Pharmaceuticals AG
Wilhelminenstrasse 91/II f/B4
1160 Vienna
Austria

8 MARKETING AUTHORISATION NUMBER

PA 0934/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2005

Date of last renewal: 13 July 2010

10 DATE OF REVISION OF THE TEXT

November 2017