



Naltrexone hydrochloride

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Opizone 50 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg naltrexone hydrochloride.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Capsule shaped, beige film-coated tablets with a score-line on one side.

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

Use in adults

Route of administration – orally with small amounts of liquid.

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

The initial dose of Opizone should be 25 mg (half a tablet) followed by the usual dose of one tablet per day (= 50 mg naltrexone hydrochloride).

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 each day till the next regular dosage-administration.

Opizone 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 Opizone.

No standard duration of treatment is stated as Opizone is an adjunctive therapy and the full recovery process in opioid-dependent patients, receiving psychological guidance as well, is individually variable. An initial period of three months should be considered, but prolonged administration may be necessary.

Opizone does not cause psychological or physical dependency. There is no attenuation in its opioid-antagonising activity in long term treatment.

Use in children and adolescents (<18 years)

Opizone 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.

Use in Elderly

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

4.3 Contraindications

- Hypersensitivity to naltrexone hydrochloride or to any of the excipients.
- Severe renal impairment.
- Severe hepatic impairment.
- Acute hepatitis.
- Opioid-dependent patients who failed detoxification because an acute withdrawal syndrome may ensue.
- Patients currently abusing opioids and with acute symptoms of withdrawal.
- Patients with withdrawal symptoms after naloxone hydrochloride administration.
- Patients with a positive urine test for opioids.

4.4 Special warnings and special precautions for use

High dose opioid intake, concomitant with Opizone treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment. Such reactions to opioids can be greater after treatment with Opizone.

Therefore a naloxone provocation test is recommended to detect the presence of any opioid use; a withdrawal syndrome precipitated by naloxone will be of shorter duration than withdrawal precipitated by Opizone.

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 Opizone-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.

Hepatic impairment is not uncommon in opioid-dependent patients.

Liver function test abnormalities have also been reported in obese and elderly patients taking Opizone who have no history of drug abuse. Opizone 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.

Should Opizone 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.

Non-opioid analgesia should be administered in case of emergent need for analgesics.

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 Opizone treatment (see section 4.3). 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 should be warned that attempts to overcome the blockade by administering large doses of opioids may after the cessation of the Opizone effect result in an acute opioid overdose, with possible fatal outcome.

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

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

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed. It is not known whether Opizone affects the metabolism of other substances. Co-administration of substances with a narrow therapeutic index must be made cautiously. In vitro studies have shown that neither naltrexone hydrochloride nor its main metabolite 6- β -naltrexol are metabolised via human CYP450 enzymes. It is therefore unlikely that the pharmacokinetics of Opizone is affected by substances inhibiting and/or inducing CYP450 enzymes. Case reports of lethargy and somnolence have been reported after the concomitant administration of naltrexone hydrochloride and thioridazine.

Patients must be warned about the use of opioids during Opizone treatment (see section 4.4).

Currently there are no known interactions between Opizone and alcohol.

4.6 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. Opizone should only be given to pregnant women when, in the judgement of the attending physician, the potential benefits outweigh the possible risk.

Lactation:

There are no clinical data on naltrexone Hydrochloride use in lactation. It is unknown whether Opizone 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

Opizone 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

Very common ($\geq 10\%$):

MedDRA system organ class	Symptom
Nervous system disorder	Headache Sleep disorders Restlessness Nervousness
Gastrointestinal disorder	Abdominal pain Abdominal cramps Nausea Inclination to vomit
Musculoskeletal and connective tissue disorders	Joint and muscle pain
General disorder and administration site conditions	Feebleness

Common ($\geq 1\%$ to $< 10\%$):

MedDRA system organ class	Symptom
Psychiatric disorders	Anxiety Increased energy Despondency Irritability Mood swings
Nervous system disorders	Thirst Dizziness Shivering Increased transpiration Vertigo
Eye disorders	Increased lacrimation
Respiratory, thoracic and mediastinal disorder	Pain in the chest
Gastrointestinal disorders	Diarrhoea Constipation
Skin and subcutaneous tissue disorder	Rash
Renal and urinary disorders	Urine retention
Reproductive system and breast disorders	Delayed ejaculation Decreased potency
General disorders and administration site conditions	Lack of appetite

Uncommon ($\geq 0.1\%$ to $< 1\%$):

No undesirable effects do apply to this category

Rare (≥ 0.01 to $< 0.1\%$):

MedDRA system organ class	Symptom
Psychiatric disorders	Depression Suicidal ideation Attempted suicide
Nervous system disorders	Speech disorder
Gastrointestinal disorders	Hepatic disorders

Very rare ($<0.01\%$)

MedDRA system organ class	Symptom
Blood and lymphatic system disorders	Idiopathic thrombocytopenic purpura
Psychiatric disorders	Agitation Euphoria Hallucination
Nervous system disorders	Tremor
Skin and subcutaneous tissue disorders	Exanthema

4.9 Overdose**Symptoms**

There is limited clinical experience with Opizone 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: Opioid antagonist

ATC code: V03A B30

Opizone is an orally effective, long-acting 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.

Opizone competitively binds to these receptors and blocks the access for exogenously administered opioids.

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

Opizone 50 mg film-coated tablet reduces the risk of relapse and supports abstinence from opioids.

Opizone 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

Opizone 50 mg film-coated tablet's active ingredient, naltrexone hydrochloride, is a specific opioid-antagonist. After oral administration Opizone is rapidly and completely absorbed from the gastrointestinal tract. Metabolism occurs in the liver to a large extent (first-pass effect) and the peak plasma concentration is reached within approximately one hour. It has a large apparent volume of distribution and 21% of the absorbed dose is bound to plasma proteins. Opizone is hydroxylated 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 Opizone is about 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.

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

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

No data are available on the pharmacokinetics of Opizone in special patients groups (children, elderly and renal impairment). Caution is advised when using Opizone in these patients (see also 4.2).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Powdered Cellulose
Croscrovidone
Microcrystalline cellulose
Silica colloidal anhydrous
Magnesium stearate

Film-coat: Opadry 31 F 27245 Beige

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000 oxide
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

Package: 7, 14, 28 tablets in PCV/PVDC blister coated with aluminium foil stored in outer carton.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 21344/0002

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