

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Targinact[▼]™ 10 mg/5 mg prolonged-release tablets

Targinact[▼]™ 20 mg/10 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Targinact 10 mg/5 mg

Each prolonged-release tablet contains:

10 mg of oxycodone hydrochloride equivalent to 9.0 mg oxycodone

5.45 mg of naloxone hydrochloride dihydrate equivalent to 5.0 mg naloxone hydrochloride and 4.5 mg naloxone.

Targinact 20 mg/10 mg

Each prolonged-release tablet contains:

20 mg of oxycodone hydrochloride equivalent to 18.0 mg oxycodone,

10.9 mg of naloxone hydrochloride dihydrate equivalent to 10.0 mg naloxone hydrochloride and 9.0 mg naloxone

Excipients:

Targinact 10 mg/5 mg

Each prolonged-release tablet contains 64.25 mg lactose monohydrate

Targinact 20 mg/10 mg

Each prolonged-release tablet contains 54.50 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Targinact 10 mg/5 mg prolonged-release tablets are oblong, white film-coated tablets, unscored and marked “OXN” on one side and “10” on the other side

Targinact 20 mg/10 mg prolonged-release tablets are oblong, pink film-coated tablets, unscored and marked “OXN” on one side and “20” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain, which can be adequately managed only with opioid analgesics

The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

4.2 Posology and method of administration

Targinact is for oral administration.

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, *Targinact* should be administered as follows:

Adults

The usual starting dose for an opioid naïve patient is 10 mg/5 mg of oxycodone hydrochloride/ naloxone hydrochloride at 12 hourly intervals. *Targinact* 10 mg/5 mg prolonged-release tablets are available for these patients. Patients requiring higher doses are recommended *Targinact* 20 mg/10 mg prolonged-release tablets.

Patients already receiving opioids may be started on higher doses of *Targinact*, depending on their previous opioid experience.

In clinical studies, only patients who had previously been dosed on oxycodone were switched to *Targinact*. To date there is no clinical experience to refer to for switching from other analgesics to *Targinact* pursuant to steps II or III of the WHO analgesic ladder.

The analgesic efficacy of *Targinact* is equivalent to oxycodone prolonged-release formulations.

The maximum daily dose of *Targinact* is limited to 40 mg/20 mg (corresponding to 40 mg oxycodone hydrochloride and 20 mg naloxone hydrochloride, or e.g. twice daily administration of *Targinact* 20 mg/10 mg prolonged-release tablets). Patients requiring higher doses should be administered supplemental prolonged-release oxycodone at the same time intervals, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be impaired.

Some patients taking *Targinact* according to a regular time schedule require immediate release analgesics as "rescue" medication for breakthrough pain. *Targinact* is not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of "rescue medication" should amount to one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two "rescues" per day is usually an indication that the dose of *Targinact* requires upward adjustment. This adjustment should be made every 1-2 days in steps of 2 x daily 10 mg/5 mg oxycodone hydrochloride/naloxone hydrochloride until a stable dose is reached. The aim is to establish a patient-specific 2 x daily dose that will maintain

adequate analgesia and make use of as little rescue medication as possible for as long as pain therapy is necessary.

Targinact is taken at the determined dosage twice daily according to a fixed time schedule. While symmetric administration (the same dose mornings and evenings) subject to a fixed time schedule (every 12 hours) is appropriate for the majority of patients, some patients, depending on the individual pain situation, may benefit from asymmetric dosing tailored to their pain pattern. In general, the lowest effective analgesic dose should be selected.

In non-malignant pain therapy, daily doses of up to 40 mg/20 mg oxycodone hydrochloride/naloxone hydrochloride (corresponding to 40 mg oxycodone hydrochloride and 20 mg naloxone hydrochloride, the twice daily administration of **Targinact** 20 mg/10mg prolonged-release tablets) are usually sufficient, but higher doses of prolonged-release oxycodone hydrochloride may be needed.

The prolonged-release tablets can be taken with or without food with sufficient liquid. **Targinact** must be swallowed whole, and not broken or chewed.

Targinact should not be administered for longer than absolutely necessary. If long-term pain treatment is necessary given the nature and severity of the illness, careful and regular monitoring is required to establish to what extent further treatment is necessary. When the patient no longer needs opioid therapy, it is advisable to taper the dose gradually.

Children (under 18 years)

Targinact is not recommended for children below the age of 18 years due to a lack of data on safety and efficacy.

Elderly patients

As for younger adults the dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Patients with impaired hepatic function

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone (see section 5.2). The clinical relevance of a relative high naloxone exposure in hepatic impaired patients is yet not known. Caution must be exercised when administering **Targinact** to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment **Targinact** is contraindicated (see section 4.3).

Patients with impaired renal function

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see section 5.2). Naloxone

concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering *Targinact* to patients with renal impairment (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients;
- Any situation where opioids are contraindicated;
- Severe respiratory depression with hypoxia and/or hypercapnoea; severe chronic obstructive pulmonary disease,
- Cor pulmonale,
- Acute severe bronchial asthma,
- Non-opioid induced paralytic ileus,
- Moderate to severe hepatic impairment.

4.4 Special warnings and precautions for use

Targinact is not suitable for the treatment of withdrawal symptoms.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, *Targinact* is expected to produce marked withdrawal symptoms - because of the opioid receptor antagonist characteristics of naloxone - or to intensify withdrawal symptoms already present (see section 4.9 - "Overdose").

Any abuse of *Targinact* by drug addicts is strongly discouraged.

Studies have not been performed on the safety and efficacy of *Targinact* in children below the age of 18 years, therefore their use in children under 18 years of age is not recommended.

Safety and efficacy of this product are not established in cancer patients and/or patients with liver metastasis.

The major risk from opioids is respiratory depression.

Caution must be exercised when administering *Targinact* to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, myxoedema, hypothyroidism, Addison's disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions, or patients taking MAO inhibitors.

Caution must also be exercised when administering *Targinact* to patients with mild hepatic or renal impairment. A careful medical monitoring is particularly necessary for patients with severe renal impairment.

The occurrence of diarrhoea should be considered as a possible effect of naloxone.

In patients under long-term opioid treatment with higher doses of opioids, the switch to *Targinact* can initially provoke withdrawal symptoms. Such patients may require specific attention.

During long-term administration, the patient may develop tolerance to the drug and require higher doses to maintain the desired analgesic effect. Chronic administration of *Targinact* may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with *Targinact* is no longer required, it may be advisable to reduce the daily dose gradually.

Targinact consists of a dual-polymer matrix, intended for oral use only. Abusive parenteral injections of the tablet constituents (especially talc) can be expected to result in local tissue necrosis and pulmonary granulomas or may lead to other serious, potentially fatal undesirable effects. In opioid addicts who abuse *Targinact*, acute withdrawal symptoms will be induced or already existing symptoms will be intensified.

In order not to impair the prolonged-release characteristic of the tablets, the tablets must be taken whole and must not be broken, chewed or crushed. Breaking, chewing or crushing the tablets for ingestion leads to a faster release of the active substances and the absorption of a possibly fatal dose of oxycodone (see Section 4.9 - "Overdose").

Targinact is not recommended for pre-operative use or within the first 12-24 hours post-operatively. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual condition of the patient, the exact timing for initiating postoperative treatment with *Targinact* depends on a careful risk-benefit assessment for each individual patient.

The empty tablet matrix may be visible in the stool.

The use of *Targinact* may produce positive results in doping controls

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take *Targinact*.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Substances having a CNS-depressant effect (e.g. alcohol, other opioids, sedatives, hypnotics, anti-depressants, sleeping aids, phenothiazines, neuroleptics, anti-

histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of *Targinact*.

Clinically relevant changes in International Normalized Ratio (INR or Quick-value) in both directions have been observed in individuals if oxycodone and coumarin anticoagulants are co-applied.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, *Targinact* is not expected to cause clinically relevant interactions with other concomitantly administered drugs metabolised over the CYP isomers CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4. In addition, the likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal.

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of *Targinact* in pregnant women and during childbirth. Limited data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of *Targinact* is relatively low (see Section 5). Both oxycodone and naloxone pass into the placenta. Animal studies have not been performed with oxycodone and naloxone in combination (see Section 5.3). Animal studies with oxycodone or naloxone administered as single drugs have not revealed any teratogenic or embryotoxic effects. Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth oxycodone may evoke respiratory depression in the newborn.

Targinact should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate.

Lactation

Oxycodone passes into the breast milk. A milk-plasma concentration ratio of 3.4:1 was measured and oxycodone effects in the suckling infant are therefore conceivable. It is not known whether naloxone also passes into the breast milk. However, after use of *Targinact* systemic naloxone levels are very low (see Section 5).

Breast-feeding should be discontinued during treatment with *Targinact*.

4.7 Effects on ability to drive and use machines

Targinact may impair the ability to drive and use machines. This is particularly likely at the beginning of treatment with *Targinact*, after dose increase or product rotation and if *Targinact* is combined with alcohol or other CNS depressant agents. Patients stabilised on a specific dosage will not necessarily be restricted. Therefore, patients should consult with their physician as to whether driving or the use of machinery is permitted.

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Uncommon: Hypersensitivity

Metabolism and nutrition disorders

Common: Decreased appetite up to loss of appetite

Psychiatric disorders

Common: Anxiety, restlessness

Uncommon: Abnormal thinking, confusion, depression, hallucination

Nervous system disorders

Common: Headache, sedation, tremor

Uncommon: Disturbance in attention, paraesthesia, speech disorder

Rare: Convulsions (particularly in persons with epileptic disorder or predisposition to convulsions)

Unknown: Syncope

Eye disorders

Uncommon: Visual disturbances

Ear and labyrinth disorders

Common: Vertigo

Cardiac disorders

Uncommon: Angina pectoris in particular in patients with history of coronary artery disease, palpitations

Vascular disorders

Common: Decrease in blood pressure

Uncommon: Increase in blood pressure

Respiratory, thoracic and mediastinal disorders

Common: Rhinorrhoea, yawning

Uncommon: Dyspnoea

Gastrointestinal disorders

Common: Abdominal pain, diarrhoea, dry mouth, flatulence, vomiting, nausea

Unknown: Constipation

Hepatobiliary disorders

Unknown: Biliary colic

Reproductive system and breast disorders

Uncommon: Erectile dysfunction

Skin and subcutaneous tissue disorders

Common: Pruritus, skin reactions, hyperhidrosis

Musculoskeletal and connective tissue disorders

Common: Muscle spasms, muscle twitching, myalgia

General disorders and application site conditions

Common: Drug withdrawal syndrome, feeling hot and cold, chills, asthenic conditions

Uncommon: Chest pain, insomnia, malaise, peripheral oedema

Injury, poisoning and procedural complications

Uncommon: Injuries from accidents

For the active substance oxycodone, the following additional undesirable effects are known:

Due to its pharmacological properties, oxycodone may cause respiratory depression, miosis, bronchial spasm and spasms of nonstriated muscles as well as suppress the cough reflex.

Infections and infestations

Rare: Herpes simplex

Immune system disorders

Very rare: Anaphylactic reaction

Metabolism and nutrition disorders

Rare: Dehydration, increased appetite

Psychiatric disorders

Common: Altered mood and personality change (e.g. depression, euphoric mood), decreased activity, psychomotor hyperactivity, agitation, nervousness, insomnia, abnormal thinking, confusion

Uncommon: Perception disturbances (e.g. hallucination, derealisation), reduced libido

The development of psychological dependence on opioid analgesics in properly managed patients with pain has been reported to be rare. However, there are no data to establish the true incidence of psychological dependence in chronic pain patients.

Nervous system disorders

Very common: Sedation (somnolence up to a depressed level of consciousness), dizziness, headache

Common: Syncope, paraesthesia

Uncommon: Migraine, dysgeusia, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination

Ear and labyrinth disorders

Uncommon: Hearing impaired

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Uncommon: Vasodilatation

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea

Uncommon: Dysphonia, cough

Gastrointestinal disorders

Very common: Constipation, vomiting, nausea

Common: Hiccups, dyspepsia

Uncommon: Mouth ulceration, stomatitis

Rare: Melaena, tooth disorder, gingival bleeding, dysphagia

Very rare: Ileus

Hepatobiliary disorders

Uncommon: Biliary colic

Very rare: Hepatic enzymes increased

Skin and subcutaneous tissue disorders

Very common: Pruritus

Rare: Dry skin

Very rare: Urticaria

Renal and urinary disorders

Common: Urinary retention, dysuria, micturition urgency

Reproductive system and breast disorders

Rare: Amenorrhoea

General disorders and administration site conditions

Uncommon: Pain, oedema

Rare: Weight increase, weight decrease, thirst

Unknown: Drug tolerance

4.9 Overdose

Symptoms and intoxication:

Depending on the history of the patient, an overdose of **Targinact** may be manifested by symptoms that are either triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist).

Symptoms of oxycodone overdose include miosis, respiratory depression, somnolence progressing to stupor, skeletal muscle flaccidity, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more severe cases and may lead to a fatal outcome.

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxications:

Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely-supervised environment.

Clinical symptoms suggestive of an oxycodone overdose may be treated by the administration of opioid antagonists (e.g. naloxone 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

Supportive measures (artificial ventilation, oxygen, vasopressors and infusions) should be employed, as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Oxycodone hydrochloride:

Pharmacotherapeutic group: Natural opium alkaloids

Naloxone hydrochloride:

Pharmacotherapeutic group: Opioid receptor antagonists

Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the CNS. By contrast, naloxone is a pure antagonist acting on all types of opioid receptors.

Because of the pronounced first-pass metabolism, the bioavailability of naloxone upon oral administration is <3%, therefore a clinically relevant systemic effect is unlikely. Due to the local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut, naloxone reduces the bowel function disorders that are typical for opioid treatment.

In a 12 weeks parallel controlled, blinded study in 322 patients with opioid-induced constipation, patients who were treated with oxycodone-naloxone had on average one extra spontaneous bowel movement in the last week of treatment, compared to patients who continued using similar doses of oxycodone prolonged release tablets ($p < 0.0001$). The use of laxatives in the first four weeks was significantly lower in the oxycodone-naloxone group compared to the oxycodone monotherapy group (31% versus 55%, respectively, $p < 0.0001$).

Compared to immediate release oxycodone preparations, *Targinact* tablets relieve pain for a considerably longer period of time.

Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.

Preclinical studies show differing effects of natural opioids on components of the immune system. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects on the immune system to natural opioids.

5.2 Pharmacokinetic properties

Oxycodone hydrochloride

Absorption

Oxycodone has a high absolute bioavailability of up to 87% following oral administration.

Distribution

Following absorption, oxycodone is distributed throughout the entire body. Plasma protein binding is approximately 45%. Oxycodone also crosses the placenta and may be detected in breast milk.

Metabolism

Oxycodone is metabolised in the liver, via the cytochrome P450-dependent enzyme system, to noroxycodone, oxymorphone, noroxymorphone and various glucuronides. Oxycodone is metabolised to noroxycodone primarily via CYP3A4 enzymes and to oxymorphone via CYP2D6. Both metabolites are further converted to Noroxymorphone. The formation of noroxymorphone is catalysed by recombinant CYP2D6 and CYP3A4 from noroxycodone and oxymorphone, respectively. CYP3A4 is the major CYP isoform responsible for noroxycodone formation, followed by CYP2B6, CYP2C9, CYP2C19, and CYP2D6. CYP2D6 is the major CYP isoform responsible for oxymorphone formation followed by CYP2C19. The analgesic effects of these metabolites are thought to be clinically insignificant. Noroxymorphone, with its high receptor potency and relative abundance in plasma may contribute to the pharmacodynamics of oxycodone. However, due to its low lipophilicity and its low ability to cross the blood-brain barrier, its prevalence in the brain is minimal.

Elimination

Oxycodone and its metabolites are excreted in both urine and faeces.

The plasma concentrations of oxycodone are only nominally affected by age, i.e. 15% higher concentrations in elderly patients than in young subjects. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a bodyweight-adjusted basis.

When compared to healthy subjects, patients with mild to severe hepatic dysfunction may demonstrate higher plasma concentrations of oxycodone and noroxycodone, and lower concentrations of oxymorphone. There may be an increase in the elimination half-life of oxycodone that could be accompanied by enhanced efficacy.

When compared to healthy subjects, patients with mild to severe renal dysfunction (creatinine clearance < 60 ml/min) may show higher plasma concentrations of oxycodone and its metabolites. There may be an increase in the elimination half-life of oxycodone that could be accompanied by enhanced efficacy.

Naloxone hydrochloride

Absorption

Following oral administration, naloxone has a very low systemic availability of <3%.

Distribution

Naloxone passes into the placenta. It is not known, whether naloxone also passes into breast milk.

Metabolism & Elimination

After parenteral administration, the plasma half-life is approximately one hour. The duration of action depends upon the dose and route of administration, intramuscular injection producing a more prolonged effect than intravenous doses. It is metabolised in the liver and excreted in the urine. The principal metabolites are naloxone glucuronide, 6 β -Naloxol and its glucuronide.

Oxycodone hydrochloride/ naloxone hydrochloride combination (***Targinact***)

Pharmacokinetics of the combination

The pharmacokinetic characteristics of oxycodone from ***Targinact*** is equivalent to those of prolonged-release oxycodone tablets (***OxyContin***®) administered together with prolonged-release naloxone tablets.

The interchangeability of the two strengths (***Targinact*** 10 mg/5mg and ***Targinact*** 20 mg/10mg prolonged-release tablets) has been demonstrated.

After the oral administration of ***Targinact*** in maximum dose, the plasma concentrations of naloxone are so low that it is not feasible to carry out a pharmacokinetic analysis. However, it is possible to conduct a pharmacokinetic analysis of naloxone-3-glucuronide as surrogate marker, since the plasma concentration is high enough to measure.

The maximum plasma concentration and bioavailability of oxycodone after ingestion of ***Targinact*** following a high-fat breakfast was approximately 15-20% higher compared to administration in the fasting state. This was evaluated as clinically not relevant, therefore ***Targinact*** may be taken with or without food (see section 4.2 Posology and method of administration).

Drug interactions

In vitro drug metabolism studies have indicated that the occurrence of clinically relevant interactions involving **Targinact** is unlikely.

Patients with impaired hepatic function

Oxycodone:

For AUCIN of oxycodone, on average there was an increase to 143% (90% C.I.: 111, 184), 319% (90% C.I.: 248, 411) and 310% (90% C.I.: 241, 398) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 120% (90% C.I.: 99, 144), 201% (90% C.I.: 166, 242) and 191% (90% C.I.: 158, 231) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For t_{1/2Z} of oxycodone, on average there was an increase to 108% (90% C.I.: 70, 146), 176% (90% C.I.: 138, 215) and 183% (90% C.I.: 145, 221) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Naloxone:

For AUC_t of naloxone, on average there was an increase to 411% (90% C.I.: 152, 1112), 11518% (90% C.I.: 4259, 31149) and 10666% (90% C.I.: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 193% (90% C.I.: 115, 324), 5292% (90% C.I.: 3148, 8896) and 5252% (90% C.I.: 3124, 8830) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available t_{1/2Z} and the corresponding AUCIN of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values.

Naloxone-3-glucuronide:

For AUCIN of naloxone-3-glucuronide, on average there was an increase to 157% (90% C.I.: 89, 279), 128% (90% C.I.: 72, 227) and 125% (90% C.I.: 71, 222) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 141% (90% C.I.: 100, 197), 118% (90% C.I.: 84, 166) and a decrease to 98% (90% C.I.: 70, 137) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For t_{1/2Z} of naloxone-3-glucuronide, on average there was an increase to 117% (90% C.I.: 72, 161), a decrease to 77% (90% C.I.: 32, 121) and a decrease to 94% (90% C.I.: 49, 139) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Patients with impaired renal function

Oxycodone:

For AUCIN of oxycodone, on average there was an increase to 153% (90% C.I.: 130, 182), 166% (90% C.I.: 140, 196) and 224% (90% C.I.: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 110% (90% C.I.: 94, 129), 135% (90% C.I.: 115, 159) and 167% (90% C.I.: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For t_{1/2Z} of oxycodone, on average there was an increase to 149%, 123%

and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone:

For AUC_t of naloxone, on average there was an increase to 2850% (90% C.I.: 369, 22042), 3910% (90% C.I.: 506, 30243) and 7612% (90% C.I.: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 1076% (90% C.I.: 154, 7502), 858% (90% C.I.: 123, 5981) and 1675% (90% C.I.: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available t_{1/2Z} and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide:

For AUC_{INF} of naloxone-3-glucuronide, on average there was an increase to 220% (90% C.I.: 148, 327), 370% (90% C.I.: 249, 550) and 525% (90% C.I.: 354, 781) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 148% (90% C.I.: 110, 197), 202% (90% C.I.: 151, 271) and 239% (90% C.I.: 179, 320) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For t_{1/2Z} of naloxone-3-glucuronide, on average there was no significant change between the renally impaired subjects and the healthy subjects.

Abuse

To avoid damage to the prolonged-release properties of the tablets, *Targinact* must not be broken, crushed or chewed, as this leads to a faster release of the active substances. In addition, following intra-nasal administration, naloxone has significant systemic bioavailability and a slow elimination rate when administered intranasally. These properties mean that abuse of *Targinact* will not have the effect intended. In oxycodone-dependent rats, the intravenous administration of oxycodone/ naloxone at a ratio of 2:1 resulted in withdrawal symptoms.

5.3 Preclinical safety data

There are no data from studies on reproductive toxicity of the combination of oxycodone and naloxone. Studies with the single components showed that oxycodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone

was not teratogenic and/or embryo/foetotoxic, and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone produced increased pup deaths in the immediate post-partum period at dosages that produced significant toxicity in maternal rats (e.g., body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Long-term carcinogenicity studies with oxycodone/naloxone in combination or oxycodone as single entity were not performed. Naloxone was not carcinogenic in a long-term study in rats.

Oxycodone and naloxone as single entities show a clastogenic potential in *in vitro* assays. No similar effects were observed, however, under *in vivo* conditions, even at toxic doses. The results indicate that the mutagenic risk of ***Targinact*** to humans at therapeutic concentrations may be ruled out with adequate certainty.

For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is not carcinogenic under these conditions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone K30,
Ethylcellulose N45,
Stearyl alcohol,
Lactose monohydrate,
Talc,
Magnesium stearate

Targinact 10 mg/5 mg

Tablet coat

Poly(vinylalcohol),
Titanium dioxide (E171),
Macrogol 3350,
Talc

Targinact 20 mg/10 mg

Tablet coat:

Poly(vinylalcohol),
Titanium dioxide (E171),

Macrogol 3350,
Talc
Iron (III) oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polyvinylchloride/aluminium foil blisters containing 56 prolonged-release tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Ltd
Cambridge Science Park
Milton Road
Cambridge CB4 0GW

8 MARKETING AUTHORISATION NUMBER(S)

PL16950/0157-8

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

29.12.2008

10 DATE OF REVISION OF THE TEXT