PROFESSIONAL INFORMATION

SCHEDULING STATUS S6

1 NAME OF THE MEDICINE

TarginAct® 5 mg/2,5 mg

TarginAct® 10 mg/5 mg

TarginAct® 20 mg/10 mg

TarginAct® 40 mg/20 mg

Strength

5 mg/2,5 mg

10 mg/5 mg

20 mg/10 mg

40 mg/20 mg

Pharmaceutical form

Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Oxycodone hydrochloride and naloxone hydrochloride.

Quantitative declaration

Each TarginAct® 5 mg/2,5 mg contains 5 mg oxycodone hydrochloride and 2,5 mg naloxone hydrochloride. Contains lactose 71,75 mg.

Each TarginAct® 10 mg/5 mg contains 10 mg oxycodone hydrochloride and 5,0 mg naloxone hydrochloride. Contains lactose 64,25 mg.

Each TarginAct® 20 mg/10 mg contains 20 mg oxycodone hydrochloride and 10,0 mg naloxone hydrochloride. Contains lactose 54,50 mg.

Each TarginAct® 40 mg/20 mg contains 40 mg oxycodone hydrochloride and 20,0 mg naloxone hydrochloride. Contains lactose 109 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablets.

TarginAct® 5 mg/2,5 mg is a blue capsule shaped tablet, marked “OXN” on one side and “5” on the other side.

TarginAct® 10 mg/5 mg is a white capsule shaped tablet, marked “OXN” on one side and “10” on the other side.

TarginAct® 20 mg/10 mg is a pink capsule shaped tablet, marked “OXN” on one side and “20” on the other side.

TarginAct® 40 mg/20 mg is a yellow capsule shaped tablet, marked “OXN” on one side and “40” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TarginAct® is indicated for the treatment of moderate to severe pain, which requires the use of an opioid analgesic.

TarginAct® is indicated as second line symptomatic treatment of patients with severe to very severe idiopathic Restless Legs Syndrome (RLS) after failure of dopaminergic therapy.

The opioid antagonist naloxone reduces the risk of opioid induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

TarginAct® is indicated in adults only.

4.2 Posology and method of administration

Posology

TarginAct® is for oral administration and must be swallowed whole and not broken or chewed. It may be taken with or without food with sufficient liquid.

Pain

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient.

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.

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. Lower strengths are available to facilitate dose titration when initiating opioid therapy and for individual dose adjustment.

Patients already receiving opioids may be started on higher doses of TarginAct®, depending on their previous opioid experience. For patients requiring higher doses TarginAct® 20 mg/10 mg or TarginAct® 40 mg/20 mg is recommended.

TarginAct® 5 mg/2,5 mg is intended for dose titration when initiating opioid therapy and individual dose adjustment.

The maximum daily dose of TarginAct® is 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.

After complete discontinuation of therapy of TarginAct® and subsequent switch to another opioid, a worsening of the bowel function can be expected.

Some patients taking TarginAct® according to a regular time schedule may require immediate-release analgesics as "rescue" medication for breakthrough pain. TarginAct® is a prolonged-release formulation and therefore not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of “rescue medication” should approximate 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 twice daily 5 mg/2,5 mg, or where necessary 10 mg/5 mg, oxycodone hydrochloride/naloxone hydrochloride until a stable dose is reached.
The aim is to establish a patient-specific, twice 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.

Restless Legs Syndrome

TarginAct® is indicated for patients suffering from Restless Legs Syndrome (RLS) for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). TarginAct® should be used after failure of previous dopaminergic treatment. Dopaminergic treatment failure is defined as inadequate initial response, a response that has become inadequate with time, occurrence of augmentation or unacceptable tolerability despite adequate doses. Previous treatment with at least one dopaminergic medicinal product should have lasted in general 4 weeks.
A shorter period might be acceptable in case of unacceptable tolerability with dopaminergic therapy.
The dosage should be adjusted to the sensitivity of the individual patient.

Treatment of patients with RLS with TarginAct® should be under the supervision of a clinician with experience in the management of RLS.

There is no clinical experience with TarginAct® in the long-term treatment of RLS beyond 1 year.

TarginAct® should be administered as follows:

Adults

The usual starting dose is 5 mg/2,5 mg of oxycodone hydrochloride / naloxone hydrochloride at 12-hourly intervals.

Titration on a weekly basis is recommended in case higher doses are required. The mean daily dose in the pivotal study was 20 mg/10 mg oxycodone hydrochloride/naloxone hydrochloride. Some patients may benefit from higher daily doses up to a maximum of 60 mg/30 mg oxycodone hydrochloride/naloxone hydrochloride.

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 situation, may benefit from asymmetric dosing tailored to the individual patient. In general, the lowest effective dose should be selected.

Special populations

Elderly patients

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

Duration of use: TarginAct® should not be administered for longer than absolutely necessary. If long-term pain treatment is necessary in view of the nature and severity of the illness, careful and regular monitoring is required to establish whether and to what extent further treatment is necessary. When the patient no longer requires opioid therapy, it may be advisable to taper the dose gradually (see section 4.4).

Adult 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).

Adult patients with impaired renal function

A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are significantly elevated in patients with renal impairment and is contraindicated (see section 5.2 and section 4.3). 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. TarginAct® is contraindicated in moderate to severe renal impairment. Caution should be exercised when administering TarginAct® to patients with mild renal impairment (see section 4.3).

Paediatric population

Children and adolescents under 18 years

The safety and efficacy of TarginAct® in patients below the age of 18 years have not been established. TarginAct® should not be used in children below the age of 18.

Method of administration

TarginAct® is for oral administration and must be swallowed whole and not broken or chewed. It may be taken with or without food with sufficient liquid.

Tablet remnants from prolonged-release formulations of the product may pass into the patient's stool; however, this finding has no clinical relevance.

Treatment goals and discontinuation

Before initiating treatment with TarginAct®, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

Oxycodone should not be used longer than absolutely necessary.

4.3 Contraindications

- TarginAct® is contraindicated in patients with known hypersensitivity to the active substances or to any of the excipients (see section 6.1);
- Any situation where opioids are contraindicated;
- Severe respiratory depression with hypoxia and/or hypercapnoea;
- Severe chronic obstructive pulmonary disease;
- Cor pulmonale;
- Severe bronchial asthma;
- Non-opioid induced paralytic ileus;
- Moderate to severe hepatic impairment;
- Moderate to severe renal impairment;
- Central sleep apnoea;
- History of opioid abuse (for patients with Restless Legs Syndrome).

4.4 Special warnings and precautions for use

Caution must be exercised when administering TarginAct® to patients with:

- opioid-induced paralytic ileus,
- severely impaired pulmonary function,
- CNS depressants co-administration (see below and section 4.5),
- Monoamine oxidase inhibitors co-administration (MAOIs, see below and section 4.5),
- psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse,
- elderly or infirm,
- tolerance, physical dependence and withdrawal (see below),
- sleep apnoea,
- 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,
- mild hepatic or renal impairment.

Respiratory depression

The major risk of all opioid excess is respiratory depression.

Sleep-related breathing disorders

Opioids, such as TarginAct®, can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxaemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage. Opioids may also cause worsening of pre-existing central sleep apnoea (see section 4.8). TarginAct® is not recommended for patients who present with CSA.

Caution must also be exercised when administering TarginAct® to patients with mild hepatic or renal impairment (see section 4.3).

Diarrhoea may occur as a possible effect of naloxone.

CNS depressant co-administration

Concomitant use of TarginAct® and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe TarginAct® concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

MAOIs

TarginAct® must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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.

TarginAct® is not suitable for the treatment of withdrawal symptoms.

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 in order to avoid the occurrence of withdrawal syndrome.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as oxycodone. Repeated use of TarginAct® can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of TarginAct® may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with TarginAct® and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active medicines (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Parenteral abuse

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).

TarginAct® consists of a dual-polymer matrix, intended for oral use only.

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must be taken whole and must not be broken, chewed or crushed. Breaking, chewing or crushing the prolonged-release 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). In addition, naloxone has a slower elimination rate when administered intranasally.

Opioids such as oxycodone may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

There is no clinical experience in patients with cancer associated to peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of TarginAct® in this population is not recommended.

The empty prolonged-release tablet matrix may be visible in the stool.

The use of TarginAct® may produce positive results in doping controls. The use of TarginAct® as a doping agent may become a health hazard.

TarginAct® is not recommended for pre-operative use or within the first 12-24 hours postoperatively.

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect

(see section 4.4). Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid moiety) (see sections 4.2). Hyperalgesia that will not respond to a further dose increase of oxycodone may occur in particular in high doses. An oxycodone dose reduction or change in opioid may be required.

Biliary tract disorders

Oxycodone can cause an increase in intrabiliary pressure and spasm as a result of its effects on the sphincter of Oddi; therefore, monitor patients with diseases of the biliary tract for worsening symptoms while administering oxycodone.

Paediatric population

There is no experience with the use of TarginAct® in children.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed in adults.

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicine increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use

should be limited (see section 4.4). Medicines which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (incl. benzodiazepines), antipsychotics, antidepressants, phenothiazines and alcohol.

TarginAct® must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone.

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson medicines) may result in increased anticholinergic adverse effects. Oxycodone is metabolised primarily via the CYP3A4 and partly via the CYP2D6 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered medicines or dietary elements. TarginAct® doses may need to be adjusted accordingly. CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g.

ritonavir) and grapefruit juice, may cause decreased clearance of oxycodone, which could lead to an increase in oxycodone plasma concentrations. CYP3A4 inducers, such as rifampin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the medicine, resulting in a decrease in oxycodone plasma concentrations.

Medicines that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone, which could lead to an increase in oxycodone plasma concentrations.

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 Fertility, pregnancy and lactation

Pregnancy

TarginAct® is not recommended for use in pregnancy or during labour. Both oxycodone and naloxone pass into the placenta.

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.

Breastfeeding

TarginAct® should not be used in mothers breastfeeding their infants as oxycodone passes into the breast milk.

Fertility

No human data on the effect of oxycodone and naloxone on fertility are available. In rats, there was no effect on mating or fertility during treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

TarginAct® can 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. Patients should consult with their medical practitioner as to whether driving or the use of machinery is permitted.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The reactions are listed as MedDRA preferred term by system organ class and absolute 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).

Immune system disorders	
Uncommon	hypersensitivity
Metabolism and nutrition disorders	
Common	decreased appetite up to loss of appetite
Psychiatric disorders	
Common	restlessness, insomnia
Uncommon	abnormal thinking, anxiety, confusional state, depression, libido decreased, euphoric mood, hallucination, nervousness
Rare	nightmares
Very rare	aggression
Not known	drug dependence (see section 4.4)
Nervous system disorders	
Common	dizziness, headache, somnolence

Uncommon	convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), disturbance in attention, paraesthesia, dysgeusia, speech disorder, syncope tremor, lethargy
Rare	sedation
Eye disorders	
Uncommon	visual impairment
Ear and labyrinth disorders	
Common	vertigo
Cardiac disorders	
Uncommon	angina pectoris in particular in patients with a history of coronary artery disease, palpitations (in the context of withdrawal syndrome)
Rare	tachycardia
Vascular disorders	
Common	hot flush, decrease in blood pressure
Uncommon	blood pressure increased
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea, rhinorrhoea, cough
Rare	yawning
Very rare	respiratory depression, central sleep apnoea syndrome
Gastrointestinal disorders	
Common	abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, vomiting, nausea
Uncommon	abdominal distension, eructation
Rare	tooth disorder
Hepatobiliary disorders	
Common	increased hepatic enzymes
Uncommon	biliary colic

Reproductive system and breast disorders	
Uncommon	erectile dysfunction
Skin and subcutaneous tissue disorders	
Common	pruritus, rash, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Uncommon	muscle spasms, muscle twitching, myalgia
Renal and urinary disorders	
Uncommon	micturition urgency
Rare	urinary retention
General disorders and administration site conditions	
Common	feeling hot and cold, chills, asthenia, fatigue
Uncommon	chest pain, malaise, pain, oedema peripheral, weight decrease, thirst
Rare	weight increase
Not known	drug withdrawal syndrome
Injury and poisoning	
Uncommon	injuries from accidents

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

The following additional undesirable effects are known for the active substance oxycodone hydrochloride.

Infections and infestations	
Rare	herpes simplex
Immune system disorders	
Very rare	anaphylactic responses
Metabolism and nutrition disorders	
Uncommon	dehydration

Rare	increased appetite
Psychiatric disorders	
Common	altered mood and personality change, decreased activity, psychomotor hyperactivity, agitation
Uncommon	perception disturbances (e.g. derealisation), reduced libido
Nervous system disorders	
Uncommon	concentration impaired, migraine, dysgeusia, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination
Not known	hyperalgesia
Eye disorders	
Uncommon	miosis
Ear and labyrinth disorders	
Uncommon	impaired hearing
Vascular disorders	
Uncommon	vasodilatation
Respiratory, thoracic and mediastinal disorders	
Uncommon	dysphonia
Gastrointestinal disorders	
Common	hiccups
Uncommon	mouth ulceration, stomatitis, dysphagia, ileus
Rare	melaena, gingival bleeding
Not known	dental caries
Hepatobiliary disorders	
Not known	cholestasis, sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	
Uncommon	dry skin
Rare	urticaria
Renal and urinary disorders	
Common	dysuria
Reproductive system and breast disorders	

Uncommon	hypogonadism
Rare	amenorrhoea
General disorders and administration site conditions	
Uncommon	oedema
Rare	thirst
Not known	drug withdrawal syndrome neonatal, drug tolerance

Adverse events identified through post marketing experience

Rare	Increased risk of abdominal pain, including pancreatitis has been reported.

Description of selected adverse reactions

Drug dependence

The frequencies in the above table regarding drug dependence, drug withdrawal syndrome and drug tolerance reflects that although risk is low with short term and low dose use, it is highly variable. Repeated use of TarginAct® can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4). The opioid abstinence or withdrawal syndrome (see section 4.4 as well as section 4.2) is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms may also develop, which include: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea or increased blood pressure, increased respiratory rate or increased heart rate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Alternatively report to: ZADrugSafety@mundipharma.co.za

4.9 Overdose

Symptoms of 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.

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxication

A patent airway must be maintained. 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 dysrhythmias 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

A 2.9 Other Analgesics

ATC code: N02AA55

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.

Naloxone is a pure antagonist acting on all types of opioid receptors. The absolute bioavailability of naloxone upon oral administration is < 3 %. Naloxone antagonises the opioid receptor mediated oxycodone effect.

Gastrointestinal System

Opioids may induce spasm of the sphincter of Oddi. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. The benefit of naloxone is achieved locally in the GI tract.

Endocrine System

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.

Restless Legs Syndrome

In a 12-week double-blind efficacy study, 150 patients with severe to very severe idiopathic Restless Legs Syndrome at randomisation were treated with oxycodone hydrochloride/naloxone hydrochloride. Severe syndrome is defined as IRLS score between 21 and 30, and very severe as score between 31 and 40. Patients showed a clinically relevant and a statistically significant improvement in mean IRLS score compared to placebo during the entire treatment period with a decrease in the mean IRLS score of 5.9 points compared to placebo at week 12 (assuming an effect similar to placebo completers for patients who discontinued the study representing a very conservative approach). The onset of efficacy was demonstrated from as early as week 1 of treatment. Similar results were shown for the RLS symptom severity improvement (as measured by the RLS-6-Rating scale), in quality of life as measured by a QoL-RLS questionnaire, in sleep quality (measured by MOS sleep scale), and for the proportion of IRLS score remitters. No subject had a confirmed case of augmentation during the study.

5.2 Pharmacokinetic properties

Oxycodone

Absorption: Oxycodone has an absolute bioavailability of up to 87 % following oral administration.

Distribution: Following absorption, oxycodone is distributed throughout the entire body. Approximately 45 % is bound to plasma protein. Oxycodone crosses the placenta and may be detected in breast milk.

Metabolism: Oxycodone is metabolised in the gut and the liver to noroxycodone, oxymorphone and to various glucuronide conjugates. Noroxycodone, oxymorphone and noroxymorphone are produced via the cytochrome P450 system. The analgesic effects of these metabolites are thought to be clinically insignificant.

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

Naloxone hydrochloride

Absorption: Following oral administration, naloxone has a systemic availability of < 3 %.

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

Metabolism and 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, 6β-Naloxol and its glucuronide.

Oxycodone hydrochloride/naloxone hydrochloride combination

The pharmacokinetic characteristics of oxycodone from TarginAct® are equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets. All dosage strengths of TarginAct® are interchangeable.

After the oral administration of TarginAct® in maximum dose to healthy subjects, the plasma concentrations of naloxone are so low that it is not feasible to carry out a pharmacokinetic analysis. To conduct a pharmacokinetic analysis naloxone-3-glucuronide as surrogate marker is used, since its plasma concentration is high enough to measure.

The peak plasma concentration (C_{max}) and bioavailability of oxycodone after ingestion of TarginAct® following a high-fat breakfast were increased by an average 16 % and 30 % respectively 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).

Elderly patients

Oxycodone: For AUC_T of oxycodone, on average there was an increase to 118 % (90 % C.I.: 103, 135), for elderly compared with younger volunteers. For C_{max} of oxycodone, on

average there was an increase to 114 % (90 % C.I.: 102, 127). For C_{min} of oxycodone, on average there was an increase to 128 % (90 % C.I.: 107, 152).

Naloxone: For AUC_T of naloxone, on average there was an increase to 182 % (90 % C.I.: 123, 270), for elderly compared with younger volunteers. For C_{max} of naloxone, on average there was an increase to 173 % (90 % C.I.: 107, 280). For C_{min} of naloxone, on average there was an increase to 317 % (90 % C.I.: 142, 708).

Naloxone-3-glucuronide: For AUC_T of naloxone-3-glucuronide, on average there was an increase to 128 % (90 % C.I.: 113, 147), for elderly compared with younger volunteers. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 127 % (90 % C.I.: 112, 144). For C_{min} of naloxone-3-glucuronide, on average there was an increase to 125 % (90 % C.I.: 105, 148).

Patients with impaired hepatic function

Oxycodone: For AUC_{INF} 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 AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values.

Naloxone-3-glucuronide: For AUC_{INF} 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 AUC_{INF} 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 characterise 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.

5.3 Preclinical safety data

There are no preclinical data pertaining to the genotoxicity/ carcinogenicity/ reproductive toxicity of the combination of oxycodone and naloxone at the 2:1 ratio. The data presented here are for studies with the single compounds.

Genotoxicity

Oxycodone and naloxone were each tested as single entities in *in vitro* and *in vivo* genotoxicity studies. The results from *in vitro* clastogenicity assays were equivocal, but neither oxycodone nor naloxone were mutagenic in the *in vitro* bacterial mutagenicity assay. However, when evaluated *in vivo*, oxycodone and naloxone were not genotoxic

in the mouse bone marrow micronucleus test even at doses that caused significant adverse effects. The weight of evidence indicates that the combination of oxycodone and naloxone poses minimal if any risk for human genotoxicity at systemic concentrations that are achieved therapeutically.

Carcinogenicity

Long-term carcinogenicity studies with oxycodone/naloxone in combination have not been performed.

Carcinogenicity was evaluated in a 2-year oral gavage study conducted in Sprague-Dawley rats. Oxycodone did not increase the incidence of tumours in male and female rats at doses up to 6 mg/kg/day. The doses were limited by opioid-related pharmacological effects of oxycodone.

For naloxone, a 24-month oral carcinogenicity study was performed in rats with doses up to 100 mg/kg/day and a 6-month carcinogenicity study was performed in TgrasH2 mice at doses up to 200 mg/kg/day. The results of the two studies indicate that naloxone was not carcinogenic under these conditions.

Reproductive and Developmental Toxicity

Oxycodone and naloxone were not teratogenic, even at maternally toxic doses in rats and rabbits. Oxycodone and naloxone did not affect fertility, reproductive performance or adversely affect long-term development of pups (F1 generation) born to rats treated with oxycodone during late pregnancy and lactation, with the exception of decreased body weights noted at doses associated with maternal toxicity. Moreover, neither oxycodone nor naloxone exhibited any developmental effects on pups born to the F1 generation females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core - ethylcellulose, lactose monohydrate, magnesium stearate, stearyl alcohol, talc.

TarginAct® 5 mg/2,5 mg contains hydroxypropylcellulose.

TarginAct® 10 mg/5 mg; 20 mg/10 mg and 40 mg/20 mg contain povidone K30.

Tablet coat - Polyvinylalcohol, macrogol, talc, titanium dioxide.

TarginAct® 5 mg/2,5 mg contains Brilliant blue FCF aluminium lake.

TarginAct® 10 mg/5 mg contains no additional colourant.

TarginAct® 20 mg/10 mg contains Iron oxide red.

TarginAct® 40 mg/20 mg contains Iron oxide yellow.

TarginAct® contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not take TarginAct®.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Do not remove from the outer carton until required for use.

6.5 Nature and contents of container

TarginAct® is supplied in clear PVC and silver aluminium foil blister packs of 28, which are enclosed in a cardboard carton.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd

Block D, Grosvenor Square,

Park Lane, Century City,

7441, Cape Town,

South Africa

8 REGISTRATION NUMBER(S)

South Africa: S6

TarginAct® 5 mg/2,5 mg: 46/2.9/0645

TarginAct® 10 mg/5 mg: 46/2.9/0646

TarginAct® 20 mg/10 mg: 46/2.9/0647

TarginAct® 40 mg/20 mg: 46/2.9/0648

Namibia: NS4

TarginAct® 5 mg/2,5 mg: 16/2.9/0137

TarginAct® 10 mg/5 mg: 16/2.9/0138

TarginAct® 20 mg/10 mg: 16/2.9/0139

TarginAct® 40 mg/20 mg: 16/2.9/0140

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 August 2015

10 DATE OF REVISION OF THE TEXT

26 June 2026

® = TarginAct® is a registered trademark.