PROPOSED CLEAN 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.

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.

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

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.
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 demanded 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 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 of age has 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.

4.3 Contraindications

- TarginAct® is contraindicated in patients with known 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;
- Severe bronchial asthma;

- Non-opioid induced paralytic ileus;
- Moderate to severe hepatic impairment;
- Moderate to severe renal impairment;
- Central Sleep Apnoea

4.4 Special warnings and precautions for use

The major risk of all opioid excess 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, 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.

Opioids, such as TarginAct®, may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxaemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing 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.

Tolerance, physical dependence and withdrawal

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.

During long-term administration, the patient may develop tolerance to the medicinal product 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 in order to avoid the occurrence of withdrawal syndrome.

There is potential for development of psychological dependence (addiction) to opioid analgesics. TarginAct® should be used with particular care in patients with a history of alcohol and drug abuse. Any abuse of TarginAct® by drug addicts is strongly discouraged.

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. Abusive parenteral injections of the prolonged-release 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 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 subocclusive 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.

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.

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

4.8 Undesirable effects

The reactions are listed as MeDRA preferred term by system organ class and absolute frequency.

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
Immune system disorders			hypersensitivity		
Metabolism and nutrition disorders		decreased appetite up to loss of appetite			

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
Eye disorders			visual impairment		
Ear and labyrinth disorders		vertigo			
Cardiac disorders			angina pectoris in particular in patients with a history of coronary artery disease, palpitations (in the context of withdrawal syndrome)	tachycardia	
Vascular disorders		hot flush, decrease in blood pressure	blood pressure increased		

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
Psychiatric disorders		restlessness, insomnia	abnormal thinking, anxiety, confusional state, depression, libido decreased, euphoric mood, hallucination, nervousness	nightmares, medicine dependence	aggression
Nervous system disorders		dizziness, headache, somnolence	convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), disturbance in attention, paraesthesia,	sedation	sleep apnoea syndrome

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
			dysgeusia, speech disorder, syncope tremor, lethargy		
Gastrointestinal disorders		abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, vomiting, nausea	abdominal distension, eructation	tooth disorder	
Hepatobiliary disorders		increased hepatic enzymes	biliary colic		
Reproductive system and breast disorders			erectile dysfunction		

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
Skin and subcutaneous tissue disorders		pruritus, rash, hyperhidrosis			
Musculoskeletal, connective tissue and bone disorders			muscle spasms, muscle twitching, myalgia		
Renal and urinary disorders			micturition urgency	urinary retention	
Respiratory, thoracic and mediastinal disorders			dyspnoea, rhinorrhoea, cough	yawning	respiratory depression
General disorders and		medicine withdrawal syndrome,	chest pain, malaise, pain, oedema	weight increase	

Body System	**Frequency of Occurrence**				
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %
administration site conditions		feeling hot and cold, chills, asthenia, fatigue	peripheral, weight decrease, thirst		
Injury and poisoning			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.

Body System	**Frequency of Occurrence**					
	Very Common ≥ 10 %	Common ≥ 1 % and < 10 %	Uncommon ≥ 0,1 % and < 1 %	Rare ≥ 0,01 % and < 0,1 %	Very Rare < 0,01 %	Not known (cannot be estimated from available data)
Infections and infestation				herpes simplex		
Immune system disorders					anaphylactic responses	
Metabolism and nutrition disorders			dehydration	increased appetite		

Psychiatric disorders		altered mood and personality change, decreased activity, psychomotor hyperactivity, agitation	perception disturbances (e.g. derealisation), reduced libido			
Nervous system disorders			concentration impaired, migraine, dysgeusia, hypertonia, involuntary muscle contractions, hypoaesthesia, abnormal coordination			hyperalgesia
Eye disorders			miosis			

Ear and labyrinth disorders			impaired hearing			
Vascular disorders			vasodilatation			
Respiratory, thoracic and mediastinal disorders			dysphonia			
Gastrointestinal disorders		hiccups	mouth ulceration, stomatitis, dysphagia, ileus	melaena, gingival bleeding		dental caries
Hepatobiliary disorders						cholestasis
Skin and subcutaneous tissue disorders			dry skin	urticaria		
Renal and urinary disorders		dysuria				

Reproductive system and breast disorders			hypogonadism	amenorrhoea		
General disorders and administration site conditions			oedema, medicine tolerance	thirst		medicine withdrawal syndrome neonatal

c. Description of selected adverse reactions

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 includes: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea or increased blood pressure, increased respiratory rate or increased heart rate.

Adverse reactions from spontaneous reporting

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04**

Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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.

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxication

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.

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.

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® is 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 tumors 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

10 March 2022