PACKAGE INSERT

SCHEDULING STATUS: S6

PROPRIETARY NAMES AND DOSAGE FORMS:

TarginAct® 5 mg/2,5 mg Prolonged Release Tablets

TarginAct® 10 mg/5 mg Prolonged Release Tablets

TarginAct® 20 mg/10 mg Prolonged Release Tablets

TarginAct® 40 mg/20 mg Prolonged Release Tablets

COMPOSITION:

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.

Inactive ingredients:

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.

PHARMACOLOGICAL CLASSIFICATION:

A 2.9 Other Analgesics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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 **DOSAGE & DIRECTIONS FOR USE**).

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.

INDICATIONS:

TarginAct® is indicated for the treatment of severe pain, which requires the use of a strong opioid analgesic and to reduce the risk of constipation.

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.

WARNINGS and SPECIAL PRECAUTIONS:

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, 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.

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

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

Diarrhoea may occur 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.

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 **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**).

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT). In addition, naloxone has a slower elimination rate when administered intranasally.

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.

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.

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

INTERACTIONS:

No interaction studies have been performed in adults.

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 warfarin are co-administered.

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.

PREGNANCY AND LACTATION:

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.

Oxycodone passes into the breast milk. It is not known whether naloxone also passes into the breast milk. **TarginAct®** should therefore not be used in mothers breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE:

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.

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.

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®** is not recommended for use in children and adolescents below the age of 18.

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 **WARNINGS and SPECIAL PRECAUTIONS**).

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 **PHARMACOKINETIC PROPERTIES**). 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 **WARNINGS and SPECIAL PRECAUTIONS**). In patients with moderate and severe hepatic impairment **TarginAct®** is contraindicated (see **CONTRAINDICATIONS**).

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 **PHARMACOKINETIC PROPERTIES** and **CONTRAINDICATIONS**). 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 **CONTRAINDICATIONS**).

SIDE 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			hypersensiti-vity		
Metabolism and nutrition disorders		decreased appetite up to loss of appetite			

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		
Psychiatric disorders		restlessness, insomnia	abnormal thinking, anxiety, confusional state, depression, libido	nightmares, medicine dependence	

			decreased, euphoric mood, hallucination, nervousness		
Nervous system disorders		dizziness, headache, somnolence	convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), disturbance in attention, paraesthesia, dysgeusia, speech disorder, syncope tremor, lethargy	sedation	
Gastrointestinal disorders		abdominal pain, constipation, diarrhoea, dry mouth,	abdominal distension, eructation	tooth disorder	

		dyspepsia, flatulence, vomiting, nausea			
Hepatobiliary disorders		increased hepatic enzymes	biliary colic		
Reproductive system and breast disorders			erectile dysfunction		
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	chest pain, malaise, pain,	weight increase	

administration site conditions		syndrome, feeling hot and cold, chills, asthenia, fatigue	oedema 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 the available data)
Infections and infestations				herpes simplex		

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 the available data)
Immune system disorders					anaphylactic responses	
Metabolism and nutrition disorders			dehydration	increased appetite		
Psychiatric disorders		altered mood and personality change, decreased activity, psycho-motor hyperactivity, agitation	perception disturbances (e.g. derealisation), reduced libido			aggression
Nervous system disorders			concentration impaired, migraine, dysgeusia, hypertonia,			hyperalgesia

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 the available data)
			involuntary muscle contractions, hypoaesthesia, abnormal coordination			
Eye disorders			miosis			
Ear and labyrinth disorders			impaired hearing			
Vascular disorders			vasodilatation			
Respiratory, thoracic and mediastinal disorders			dysphonia			
Gastrointestinal disorders		hiccups	mouth ulceration, stomatitis,	melaena, gingival bleeding		dental caries

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 the available data)
			dysphagia, ileus			
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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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.

PRESENTATION:

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

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Do not remove from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Mundipharma (Pty) Ltd

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Park Lane, Century City,

7441

South Africa

www.mundipharma.co.za

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 06 August 2015

Date of the most recently revised package insert as approved by the Authority: 17 August 2018

® = **TarginAct** is a registered trademark.