SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Product Name] 5 mg/2.5 mg prolonged-release tablets
[Product Name] 10 mg/5 mg prolonged-release tablets
[Product Name] 20 mg/10 mg prolonged-release tablets
[Product Name] 30 mg/15 mg prolonged-release tablets
[Product Name] 40 mg/20 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Product Name] 5 mg/2.5 mg
Each prolonged-release tablet contains 5 mg oxycodone hydrochloride (equivalent to 4.5 mg oxycodone) and 2.5 mg naloxone hydrochloride (as 2.74 mg naloxone hydrochloride dihydrate equivalent to 2.25 mg naloxone).

[Product Name] 10 mg/5 mg
Each prolonged-release tablet contains 10 mg oxycodone hydrochloride (equivalent to 9 mg oxycodone) and 5 mg naloxone hydrochloride (as 5.45 mg naloxone hydrochloride dihydrate equivalent to 4.5 mg naloxone).

[Product Name] 20 mg/10 mg
Each prolonged-release tablet contains 20 mg oxycodone hydrochloride (equivalent to 18 mg oxycodone) and 10 mg naloxone hydrochloride (as 10.9 mg naloxone hydrochloride dihydrate equivalent to 9 mg naloxone).

[Product Name] 30 mg/15 mg
Each prolonged-release tablet contains 30 mg oxycodone hydrochloride (equivalent to 27 mg oxycodone) and 15 mg naloxone hydrochloride (as 16.35 mg naloxone hydrochloride dihydrate equivalent to 13.5 mg naloxone).

[Product Name] 40 mg/20 mg
Each prolonged-release tablet contains 40 mg oxycodone hydrochloride (equivalent to 36 mg oxycodone) and 20 mg naloxone hydrochloride (as 21.8 mg naloxone hydrochloride dihydrate equivalent to 18 mg naloxone).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

[Product Name] 5 mg/2.5 mg
White, round, biconvex prolonged-release tablet with a diameter of 4.7 mm and a height of 2.9 - 3.9 mm.

[Product Name] 10 mg/5 mg
Pink, oblong, biconvex prolonged-release tablet with break scores on both sides, with a length of 10.2 mm, a width of 4.7 mm and a height of 3.0 - 4.0 mm.
The tablet can be divided into equal doses.

[Product Name] 20 mg/10 mg
White, oblong, biconvex prolonged-release tablet with break scores on both sides, with a length of 11.2 mm, a width of 5.2 mm and a height of 3.3 - 4.3 mm.
The tablet can be divided into equal doses.

[Product Name] 30 mg/15 mg
Yellow, oblong, biconvex prolonged-release tablet with break scores on both sides, with a length of 12.2 mm, a width of 5.7 mm and a height of 3.3 - 4.3 mm.
The tablet can be divided into equal doses.

[Product Name] 40 mg/20 mg
Pink, oblong, biconvex prolonged-release tablet with break scores on both side, with a length of 14.2 mm, a width of 6.7 mm and a height of 3.6 - 4.6 mm
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.

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

[Product Name] is indicated in adults.

4.2 Posology and method of administration

Posology

Analgesia
The analgesic efficacy of [Product Name] is equivalent to oxycodone hydrochloride prolonged-release formulations.

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient. Unless otherwise prescribed, [Product Name] should be administered as follows:

Adults
The usual starting dose for an opioid naive 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 [Product Name] depending on their previous opioid experience.

The maximum daily dose of [Product Name] is 160 mg oxycodone hydrochloride and 80 mg naloxone hydrochloride. The maximum daily dose is reserved for patients who have previously been maintained on a stable daily dose of [Product Name] and who have become in need of an increased dose. Special attention should be given to patients with compromised renal function and patients with mild hepatic impairment if an increased dose is considered. For patients requiring higher doses of [Product Name],

administration of supplemental prolonged-release oxycodone hydrochloride at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone hydrochloride. In the case of supplemental oxycodone hydrochloride dosing, the beneficial effect of naloxone hydrochloride on bowel function may be impaired.

After complete discontinuation of therapy with [Product Name] with a subsequent switch to another opioid a worsening of the bowel function can be expected.

Some patients taking [Product Name] according to a regular time schedule require immediate-release analgesics as "rescue" medication for breakthrough pain. [Product Name] 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 [Product Name] requires upward adjustment. This adjustment should be made every 1-2 days in steps of 5 mg/2.5 mg twice daily, 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.

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

In non-malignant pain therapy, daily doses of up to 40 mg/20 mg oxycodone hydrochloride/naloxone hydrochloride are usually sufficient, but higher doses may be needed.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Restless legs syndrome

[Product Name] is indicated for patients suffering from RLS for at least 6 months. RLS symptoms should be present daily and during daytime (≥ 4 days/week). [Product Name] 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 restless legs syndrome with [Product Name] should be under the supervision of a clinician with experience in the management of restless legs syndrome.

Unless otherwise prescribed, [Product Name] 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 20mg/10mg 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.

[Product Name] 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.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Analgesia / Restless legs syndrome

Elderly patients
As for younger adults the dosage should be adjusted to the intensity of the pain or RLS symptoms and the sensitivity of the individual patient.

Hepatic impairment
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 [Product Name] to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment [Product Name] is contraindicated (see section 4.3).

Renal impairment
A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment (see section 5.2). Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. Caution should be exercised when administering [Product Name] to patients with renal impairment (see section 4.4).

Paediatric population
The safety and efficacy of [Product Name] in children aged below 18 years has not been established. No data are available.

Method of administration
For oral use.

[Product Name] is taken in the determined dosage twice daily in a fixed time schedule.

The prolonged-release tablets may be taken with or without food with sufficient liquid.

[Product Name] 5 mg/2.5 mg
The prolonged-release tablet must be swallowed whole and must not be divided, broken, chewed or crushed.
[Product Name] 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg, 40 mg/20 mg
The prolonged-release tablet can be divided into equal doses but must not be chewed or crushed.

Duration of use
[Product Name] should not be administered for longer than absolutely necessary. If long-term 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.

Analgesia

When the patient no longer requires opioid therapy, it may be advisable to taper the dose gradually (see section 4.4).

Restless legs syndrome
At least every three months during therapy with [Product Name] patients should be clinically evaluated. Treatment should only be continued if [Product Name] is considered effective and the benefit is considered to outweigh adverse effects and potential harms in individual patients. Prior to continuation of RLS treatment beyond 1 year a discharge regimen by gradually tapering down of [Product Name] over a period of approximately one week should be considered to establish if continued treatment with [Product Name] is indicated.

When a patient no longer requires opioid therapy cessation of treatment by tapering down over a period of approximately one week is recommended in order to reduce the risk of a withdrawal reaction (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1,
- Severe respiratory depression with hypoxia and/or hypercapnia,
- Severe chronic obstructive pulmonary disease,
- Cor pulmonale,
- Severe bronchial asthma,
- Non-opioid induced paralytic ileus,
- Moderate to severe hepatic impairment.

Additionally for restless legs syndrome:
- History of opioid abuse

4.4 Special warnings and precautions for use

Caution must be exercised when administering [Product Name] to patients:
- with severely impaired respiratory function
- with sleep apnoea
- taking CNS depressants (see below and section 4.5)
- taking monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- with tolerance, physical dependence and withdrawal (see below)
- with psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- elderly or infirm
- with head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- with epileptic disorder or predisposition to convulsions
- with hypotension
- with hypertension
- with pancreatitis
- with mild hepatic impairment
- with renal impairment
- with opioid-induced paralytic ileus
- with myxoedema
- with hypothyroidism
- with Addison's disease (adrenal cortical insufficiency)
- with prostate hypertrophy
- with toxic psychosis
- with alcoholism
- with delirium tremens

- with cholelithiasis
- with pre-existing cardiovascular diseases

Respiratory depression
The primary risk of opioid excess is respiratory depression.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent manner. In patients who present with CSA, consider decreasing the total opioid dosage.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of opioids, including oxycodone hydrochloride and sedative medicines such as benzodiazepines or related drugs 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 [Product Name] 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).

Caution is advised in treating restless legs syndrome patients with additional sleep apnoea syndrome with [Product Name] due to the additive risk of respiratory depression. No data about the risk exist because in the clinical trial patients with sleep apnoea syndrome were excluded.

MAOIs
[Product Name] must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

Hepatic or renal impairment
Caution must also be exercised when administering [Product Name] to patients with mild hepatic or renal impairment. Careful medical monitoring is particularly necessary for patients with severe renal impairment.

Diarrhoea
Diarrhoea may be considered as a possible effect of naloxone.

Tolerance, physical dependence and withdrawal
During long-term administration, the patient may develop tolerance to the medicinal product and require higher doses to maintain the desired effect. Chronic administration of [Product Name] may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with [Product Name] is no longer required, it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of withdrawal syndrome (see section 4.2).

[Product Name] is not suitable for the treatment of withdrawal symptoms.

There is no clinical experience with [Product Name] in the long-term treatment of RLS beyond 1 year (see section 4.2).

Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse
There is potential for development of psychological dependence (addiction) to opioid analgesics, including [Product Name]. [Product Name] should be used with particular care in patients with a history of alcohol and drug abuse. Oxycodone alone has an abuse profile similar to other strong agonist opioids.

Possibly fatal dose of oxycodone
[Product Name] 5 mg/2.5 mg
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 divided, broken, chewed or crushed. Dividing, 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).

[Product Name] 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg, 40 mg/20 mg
In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must not be chewed or crushed. 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).

Somnolence and/or an episode of sudden sleep onset
Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of the dose or termination of therapy may be considered. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products in combination with [Product Name] (see sections 4.5 and 4.7).

Alcohol
Concomitant use of alcohol and [Product Name] may increase the undesirable effects of [Product Name]; concomitant use should be avoided.

Cancer
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 [Product Name] in this population is not recommended.

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

Abuse
Any abuse of [Product Name] by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, [Product Name] 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).

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.

Effects upon the endocrine system

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.

Long-term treatment
In patients under long-term opioid treatment, the switch to [Product Name] can initially provoke withdrawal symptoms or diarrhoea. Such patients may require specific attention.

Hyperalgesia
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.

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

Doping
Athletes must be aware that this medicine may cause a positive reaction in 'anti-doping' tests. The use of [Product Name] as a doping agent may become a health hazard.

Paediatric population
Studies have not been performed on the safety and efficacy of [Product Name] in children and adolescents below the age of 18 years. Therefore, their use in children and adolescents under 18 years of age is not recommended.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).

Drugs which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), antidepressants, antipsychotics, antihistamines and antiemetics.

[Product Name] must be administered with caution in patients taking MAOIs or who have received MAOIs within the previous two weeks.

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.

Alcohol may enhance the pharmacodynamic effects of [Product Name]; concomitant use should be avoided.

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

Oxycodone is metabolised primarily via the CYP3A4 pathways and partly via the CYP2D6 pathway (see section 5.2). The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. [Product Name] doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungal agents (e.g. ketoconazole, voriconazole, itraconazole, posaconazole), protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir), cimetidine and grapefruit juice may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A reduction in the dose of [Product Name] and subsequent re-titration may be necessary.

CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin and St. John's Wort, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations. Caution is advised, and further titration may be necessary to reach an adequate level of symptom control.

Theoretically, medicinal products that inhibit CYP2D6 activity, such as paroxetine, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. Concomitant administration with CYP2D6 inhibitors had an insignificant effect on the elimination of oxycodone and also had no influence on the pharmacodynamic effects of oxycodone.

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

There are no data from the use of [Product Name] in pregnant women and during childbirth. Limited data on the use of oxycodone during pregnancy in humans reveal no evidence of an increased risk of congenital abnormalities. For naloxone, insufficient clinical data on exposed pregnancies are available. However, systemic exposure of the women to naloxone after use of [Product Name] is relatively low (see section 5.2).

Both oxycodone and naloxone pass into the placenta. Animal studies have not been performed with oxycodone and naloxone in combination (see section 5.3). Animal studies with oxycodone or naloxone administered as single drugs have not revealed any teratogenic or embryotoxic effects.

Long-term administration of oxycodone during pregnancy may lead to withdrawal symptoms in the newborn. If administered during childbirth, oxycodone may evoke respiratory depression in the newborn.

[Product Name] should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate.

Breastfeeding

Oxycodone passes into the breast milk. A milk-plasma concentration ratio of 3.4:1 was measured and oxycodone effects in the suckling infant are therefore conceivable. It is not known whether naloxone also passes into the breast milk. However, after use of [Product Name] systemic naloxone levels are very low (see section 5.2).

A risk to the suckling child cannot be excluded in particular following intake of multiple doses of [Product Name] by the breastfeeding mother.

Breastfeeding should be discontinued during treatment with [Product Name].

Fertility
There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

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

Patients being treated with [Product Name] and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also sections 4.4 and 4.5).

4.8 Undesirable effects

Undesirable effects are presented below in three sections: undesirable effects in the treatment of pain, additional undesirable effects known for the active substance oxycodone hydrochloride and undesirable effects in the treatment of restless legs syndrome.

The following frequencies are the basis for assessing undesirable effects:

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

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

Undesirable effects in the treatment of pain

System organ class MedDRA	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders		Hypersensitivity		
Metabolism and nutritional disorders	Decreased appetite up to loss of appetite			
Psychiatric disorders	Insomnia	Abnormal thinking Anxiety Confusional state Depression Libido decreased Nervousness	Drug dependence (see section 4.4.)	Euphoric mood Hallucination Nightmares Aggression

System organ class MedDRA	Common	Uncommon	Rare	Not known
		Restlessness		
Nervous system disorders	Dizziness Headache Somnolence	Convulsions[1] Disturbance in attention Dysgeusia Speech disorder Syncope Tremor Lethargy		Paraesthesia Sedation Sleep apnoea syndrome (see section 4.4)
Eye disorders		Visual impairment		
Ear and labyrinth disorders	Vertigo			
Cardiac disorders		Angina pectoris[2] Palpitations	Tachycardia	
Vascular disorders	Hot flush	Blood pressure decreased Blood pressure increased		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Rhinorrhoea Cough	Yawning	Respiratory depression
Gastrointestinal disorders	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Vomiting Nausea Flatulence	Abdominal distention	Tooth disorder	Eructation
Hepatobiliary disorders		Hepatic enzymes increased Biliary colic		
Skin and subcutaneous tissue disorders	Pruritus Skin reactions Hyperhidrosis			

System organ class MedDRA	Common	Uncommon	Rare	Not known
Musculo-skeletal and connective tissue disorders		Muscle spasms Muscle twitching, Myalgia		
Renal and urinary disorders		Micturition urgency		Urinary retention
Reproductive system and breast disorders				Erectile dysfunction
General disorders and administration site conditions	Asthenia Fatigue	Chest pain Chills Drug withdrawal syndrome Malaise Pain Peripheral oedema Thirst		
Investigations		Weight decreased	Weight increased	
Injury, poisoning, and procedural complications		Injury from accidents		

[1] particularly in persons with epileptic disorder or predisposition to convulsions
[2] particular in patients with history of coronary artery disease

<u>For the active substance oxycodone hydrochloride, the following additional undesirable effects are known</u>
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.

System organ class MedDRA	Common	Uncommon	Rare	Not known
Infections and infestations			Herpes simplex	
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders		Dehydration	Increased appetite	

Psychiatric disorders	Altered mood and personality change Decreased activity Psychomotor hyperactivity	Agitation Perception disturbances (e.g. derealisation)		
Nervous system disorders		Concentration impaired Migraine Hypertonia Involuntary muscle contractions Hypoaesthesia Abnormal co-ordination		Hyperalgesia
Ear and labyrinth disorders		Hearing impaired		
Vascular disorders		Vasodilation		
Respiratory, thoracic and mediastinal disorders		Dysphonia		
Gastrointestinal disorders	Hiccups	Dysphagia Ileus Mouth ulceration Stomatitis	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 Drug tolerance		Drug withdrawal syndrome neonatal

Undesirable effects in the treatment of restless legs syndrome

The list below reflects the adverse drug reactions seen with oxycodone hydrochloride/naloxone hydrochloride in a 12-week, randomised, placebo-controlled clinical trial comprising a total of 150

patients on oxycodone hydrochloride/naloxone hydrochloride and 154 patients on placebo with daily dosages between 10 mg/5 mg and 80 mg/40 mg oxycodone hydrochloride/naloxone hydrochloride. Adverse drug reactions associated with oxycodone hydrochloride/naloxone hydrochloride in pain and not observed in RLS study population were added with the frequency of not known.

System organ class MedDRA	**Very Common**	**Common**	**Uncommon**	**Not known**
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		Decreased appetite up to loss of appetite		
Psychiatric disorders		Insomnia Depression	Libido decreased Sleep attacks	Abnormal thinking Anxiety Confusional state Nervousness Restlessness Euphoric mood Hallucination Nightmares Drug dependence Aggression
Nervous system disorders	Headache Somnolence	Dizziness, Disturbance in attention Tremor Paraesthesia	Dysgeusia	Convulsions[1] Sedation Speech disorder Syncope Lethargy
Eye disorders		Visual impairment		
Ear and labyrinth disorders		Vertigo		
Cardiac disorders				Angina pectoris[2] Palpitations Tachycardia
Vascular disorders		Hot flush Blood pressure decreased Blood pressure increased		
Respiratory thoracic and mediastinal disorders			Dyspnoea	Cough Rhinorrhoea Respiratory depression Yawning
Gastrointestinal disorders	Constipation, Nausea	Abdominal pain, Dry mouth Vomiting	Flatulence	Abdominal Distention Diarrhea Dyspepsia Eructation Tooth disorder
Hepatobiliary disorders		Hepatic enzymes increased[3]		Biliary colic

Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus, Skin reactions		
Musculoskeletal and connective tissue disorders				Muscle spasms Muscle twitching Myalgia
Renal and urinary disorders				Micturition urgency Urinary retention
Reproductive systems and breast disorders			Erectile dysfunction	
General disorders and administration site conditions	Fatigue	Chest pain Chills Thirst Pain	Drug withdrawal syndrome Oedema peripheral	Malaise Asthenia
Investigation				Weight decreased Weight increased
Injury, poisoning and procedural complications			Injuries from accidents	

[1] particularly in persons with epileptic disorder or predisposition to convulsions
[2] in particular in patients with history of coronary artery disease
[3] alanine aminotransferase increased, gamma-glutamyl transferase increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of intoxication
Depending on the history of the patient, an overdose of [Product Name] 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, hypotonia, 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 hydrochloride 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 hydrochloride in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should be 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 fluid infusions) should be employed as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; Analgesics; opioids; natural opium alkaloids, ATC code: N02AA55

Mechanism of action
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 binds to the endogenous opioid receptors in the CNS. By contrast, naloxone is a pure antagonist acting on all types of opioid receptors.

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

Clinical efficacy and safety
For effects of opioids upon the endocrine system, see section 4.4.

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

Analgesia
In a 12 weeks parallel group double-blinded study in 322 patients with opioid-induced constipation, patients who were treated with oxycodone hydrochloride/naloxone hydrochloride had on average one extra complete spontaneous (without laxatives) bowel movement in the last week of treatment, compared to patients who continued using similar doses of oxycodone hydrochloride prolonged release tablets ($p<0.0001$). The use of laxatives in the first four weeks was significantly lower in the oxycodone-naloxone group compared to the oxycodone monotherapy group (31% versus 55%, respectively, $p<0.0001$). Similar results were shown in a study with 265 non-cancer patients comparing daily doses of oxycodone hydrochloride/naloxone hydrochloride of 60 mg/30 mg to up to 80 mg/40 mg with oxycodone hydrochloride monotherapy in the same dose range.

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 hydrochloride

Absorption

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

Distribution

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

Biotransformation

Oxycodone is metabolised in the gut and the liver to noroxycodone and oxymorphone and to various glucuronide conjugates. Noroxycodone, oxymorphone and noroxymorphone are produced via the cytochrome P450 system. Quinidine reduces the production of oxymorphone in man without substantially influencing the pharmacodynamics of oxycodone. The contribution of the metabolites to overall pharmacodynamic effect is insignificant.

Elimination

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

Naloxone hydrochloride

Absorption

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

Distribution

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

Biotransformation 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 ([Product Name])

Pharmacokinetic/pharmacodynamic relationships

The pharmacokinetic characteristics of oxycodone from [Product Name] is equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dosage strengths of [Product Name] are interchangeable.

After the oral administration of [Product Name] 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.

Overall, following ingestion of a high-fat breakfast, the bioavailability and peak plasma concentration (C_{max}) of oxycodone were increased by an average of 16% and 30% respectively compared to administration in the fasting state. This was evaluated as clinically not relevant, therefore [Product Name] prolonged-release tablets may be taken with or without food (see section 4.2).

In vitro drug metabolism studies have indicated that the occurrence of clinically relevant interactions involving [Product Name] is unlikely.

Elderly patients

Oxycodone
For AUCτ 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 AUCτ 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 AUCτ 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 t1/2Z 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.

Abuse
To avoid damage to the prolonged-release properties of the tablets, [Product Name] must not be broken, crushed or chewed, as this leads to a rapid release of the active substances. In addition, naloxone has a slower elimination rate when administered intranasally. Both properties mean that abuse of [Product Name] will not have the effect intended. In oxycodone-dependent rats, the intravenous administration of oxycodone hydrochloride/ naloxone hydrochloride at a ratio of 2:1 resulted in withdrawal symptoms.

5.3 Preclinical safety data

There are no data from studies on reproductive toxicity of the combination of oxycodone and naloxone. Studies with the single components showed that oxycodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices. The standard oral reproduction toxicity studies with naloxone show that at high oral doses naloxone was not teratogenic and/or embryo/foetotoxic, and does not affect perinatal/postnatal development. At very high doses (800 mg/kg/day) naloxone

produced increased pup deaths in the immediate post-partum period at dosages that produced significant toxicity in maternal rats (e.g. body weight loss, convulsions). However, in surviving pups, no effects on development or behaviour were observed.

Long-term carcinogenicity studies with oxycodone / naloxone in combination or oxycodone as a single entity have not been performed. For naloxone, a 24-months oral carcinogenicity study was performed in rats with naloxone doses up to 100 mg/kg/day. The results indicate that naloxone is not carcinogenic under these conditions.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Polyvinyl acetate
Povidone
Sodium laurilsulfate
Silica, colloidal anhydrous
Cellulose, microcrystalline
Magnesium stearate

Tablet coating
[Product Name] 5 mg/2.5 mg
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc

[Product Name] 10 mg/5 mg
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)

[Product Name] 20 mg/10 mg
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc

[Product Name] 30 mg/15 mg
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)

[Product Name] 40 mg/20 mg

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Bottles: Do not store above 30°C
Blister: Do not store above 25°C

6.5 Nature and contents of container

Blister
Child resistant aluminium/PVC/PE/PVDC blisters.
Child resistant aluminium/PVC/PE/PVDC perforated unit dose blisters.

Bottles
White high-density polyethylene (HDPE) bottles with white, tamper-evident child-resistant, closure made of polypropylene (PP).

Pack sizes
Blister: 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100 prolonged-release tablets
Unit dose blister: 10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 60x1, 90x1, 98x1, 100x1 prolonged-release tablets
Bottle: 50, 100, 200, 250 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

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