SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sofonac 20 mg/10 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Sofonac is indicated in adults.

4.2 Posology and method of administration

Posology

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

Analgesia

The analgesic efficacy of Sofonac is equivalent to oxycodone hydrochloride prolonged-release formulations.
The dose should be adjusted to the intensity of pain and the sensitivity of the individual patient.

Adults
The usual starting dose for an opioid naive 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 oxycodone hydrochloride/naloxone hydrochloride depending on their previous opioid experience.

Oxycodone hydrochloride/naloxone hydrochloride 5 mg/2.5 mg is intended for dose titration when initiating opioid therapy and individual dose adjustment.

The maximum daily dose 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 oxycodone hydrochloride/naloxone hydrochloride and who have become in need of an increased dose.

For patients requiring higher doses of oxycodone hydrochloride/naloxone hydrochloride, 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.

Some patients taking Sofonac according to a regular time schedule require immediate-release analgesics as “rescue” medication for breakthrough pain. Sofonac 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 Sofonac requires upward adjustment. This adjustment should be made every 1 to 2 days in steps of 5 mg/2.5 mg oxycodone hydrochloride/naloxone hydrochloride 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.

Sofonac is taken at the determined dose 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.

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

Duration of use
Sofonac should not be administered for longer than absolutely necessary.

Special populations

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

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 renally impaired patients is yet not known. Caution should be exercised when administering Sofonac to patients with renal impairment (see section 4.4) and particularly if a dose increase is considered.

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 relatively high naloxone exposure in patients with hepatic impairment is not yet known.
Caution must be exercised when administering Sofonac to patients with mild hepatic impairment (see section 4.4). Similarly, special attention is required in patients with mild hepatic impairment if an increased dose is considered.
In patients with moderate and severe hepatic impairment Sofonac is contraindicated (see section 4.3).

Paediatric population

The safety and efficacy of Sofonac in children and adolescents aged below 18 years has not been established. No data are available.

Method of administration
Oral use.

Sofonac is taken in the determined dose twice daily in a fixed time schedule. The prolonged-release tablets may be taken with or without food with sufficient liquid.

Sofonac must be swallowed whole with sufficient liquid, and must not be divided, broken, chewed or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance(s) 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.

4.4 Special warnings and precautions for use

Caution must be exercised when administering these tablets to patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Monoamine oxidase inhibitors (MAOIs, see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Elderly or infirm
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Epileptic disorder or predisposition to convulsions
- Hypotension
- Hypertension
- Pancreatitis
- Mild hepatic impairment
- Renal impairment
- Opioid-induced paralytic ileus
- Myxoedema
- Hypothyroidism
- Addison’s disease (adrenal cortical insufficiency)
- Prostate hypertrophy
- Toxic psychosis
- Alcoholism
- Delirium tremens
- Cholelithiasis

- Pre-existing cardiovascular diseases

Respiratory depression
The major 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 medicinal products such as benzodiazepines or related medicinal products
Concomitant use of Sofonac and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Sofonac concomitantly with sedative medicinal products, 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).

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

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

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

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

Hepatobiliary disorders
Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone / naloxone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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 Sofonac may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with Sofonac 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).

Sofonac is not suitable for the treatment of withdrawal symptoms.

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 Sofonac (see sections 4.5 and 4.7).

Alcohol
Concomitant use of alcohol and Sofonac may increase the undesirable effects of Sofonac; concomitant use should be avoided.

Cancer
There is no clinical data available for cancer patients with peritoneal carcinomatosis or beginning intestinal obstruction in advanced stages of digestive and pelvic cancers. Therefore, the use of Sofonac in this population is not recommended.

Surgery
Sofonac is not recommended for pre-operative use or within the first 12 to 24 hours post-operatively. Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI). 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 Sofonac depends on a careful benefit-risk assessment for each individual patient.

Precautions for proper use
In order not to impair the prolonged-release characteristic of the tablets, they 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).

Abuse

Any abuse of Sofonac by drug addicts is strongly discouraged.
If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, Sofonac 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).

Opioids, such as oxycodone hydrochloride, 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.
In patients under long-term opioid treatment with higher doses of opioids, the switch to Sofonac can initially provoke withdrawal symptoms. Such patients may require specific attention.
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.

Sofonac 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.

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

<Doping
The use of Sofonac may produce positive results in doping controls. The use of Sofonac as a doping agent may become a health hazard.>

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially ‘sodium-free’.

Paediatric population
Studies have not been performed on the safety and efficacy of oxycodone hydrochloride/naloxone hydrochloride in children and adolescents below the age of 18 years. Therefore, the use of Sofonac in children and adolescents under 18 years of age is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Substances having a CNS-depressant effect (e.g. other opioids, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) may enhance the CNS-depressant effect (e.g. respiratory depression) of Sofonac.

Sedative medicinal products such as benzodiazepines or related medicinal products
The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products 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).

Concomitant administration of oxycodone with serotonin medicinal products, 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 dose may need to be reduced in patients using these medicinal products.

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tri-cyclic antidepressants, antihistamines, anti-psychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Alcohol may enhance the pharmacodynamic effects of Sofonac; concomitant use should be avoided.

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

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 medicinal products or dietary elements. Sofonac doses may need to be adjusted accordingly.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), azole-antifungals (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 Sofonac 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 active substance, 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 oxycodone hydrochloride/naloxone hydrochloride 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 Sofonac is relatively low (see section 5.2). Both oxycodone and naloxone pass 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 active substances 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.

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

Breastfeeding
Oxycodone passes into 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 breast milk. However, after use of Sofonac 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 Sofonac by the breast-feeding mother.
Breast-feeding should be discontinued during treatment with Sofonac.

Fertility
There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

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

Patients being treated with Sofonac 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

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 nutrition disorders	Decreased appetite up to loss of appetite			
Psychiatric disorders	Insomnia	Abnormal thinking Anxiety Confusion Depression Decreased libido Nervousness Restlessness		Euphoric mood Hallucination Nightmares Aggression
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		

System organ class (MedDRA)	Common	Uncommon	Rare	Not known
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 Central sleep apnoea syndrome
Gastrointestinal disorders	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Vomiting Nausea Flatulence	Abdominal distension	Tooth disorder	Eructation
Hepatobiliary disorders		Hepatic enzymes increased Biliary colic		
Skin and subcutaneous tissue disorders	Pruritus Skin reactions Hyperhidrosis			
Musculoskeletal 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	Asthenic conditions Fatigue	Chest pain Chills Drug withdrawal syndrome Malaise Pain		

System organ class (MedDRA)	Common	Uncommon	Rare	Not known
		Oedema peripheral Thirst		
Investigations		Weight decreased	Weight increased	
Injury, poisoning, and procedural complications		Injuries from accidents		

[1] particularly in patients with epileptic disorder or predisposition to convulsions
[2] particularly 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 responses
Metabolism and nutrition disorders		Dehydration	Increased appetite	
Psychiatric disorders	Altered mood and personality changes Decreased activity Psychomotor hyperactivity	Agitation Perception disturbances (e.g. derealisation)		
Nervous system disorders		Concentration impaired Migraine Hypertonia Involuntary muscle contractions Hypoaesthesia Abnormal coordination		Hyperalgesia
Ear and		Hearing		

System organ class MedDRA	Common	Uncommon	Rare	Not known
labyrinth disorders		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, Sphincter of Oddi dysfunction
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

Drug dependence

Repeated use of Sofonac can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

Symptoms of a naloxone overdose alone are unlikely.

Therapy of intoxication
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 to 2 mg intravenously). Administration should be repeated at 2 to 3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone hydrochloride in 500 ml of sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) (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 measure (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: 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
Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.

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

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.

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

Pharmacokinetic/pharmacodynamic relationships
The pharmacokinetic characteristics of oxycodone from oxycodone hydrochloride/naloxone hydrochloride prolonged-release tablets is equivalent to those of prolonged-release oxycodone hydrochloride tablets administered together with prolonged-release naloxone hydrochloride tablets.

All dose strengths of Sofonac are interchangeable.

After the oral administration of oxycodone hydrochloride/naloxone hydrochloride 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 Sofonac 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 oxycodone hydrochloride/naloxone hydrochloride is unlikely.

Elderly

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).

Hepatic Impairment

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 AUCτ 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 AUCτ 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.

Renal Impairment

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 AUCτ 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 AUCτ values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

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

Abuse
To avoid damage to the prolonged-release properties of the tablets, Sofonac 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 Sofonac 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 doses 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 Sofonac 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 K30
Sodium lauryl sulphate
Silica, colloidal anhydrous

Cellulose, microcrystalline
Magnesium stearate

Tablet coating
Polyvinyl alcohol,
Titanium dioxide (E171),
Iron oxide yellow (E 172),
Macrogol 3350,
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container

Child resistant blisters (aluminium//PVC/PE/PVDC).

Pack sizes
28, 56 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

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Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0087

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/11/2021

10 DATE OF REVISION OF THE TEXT

07/03/2025