Approved Professional Information for Medicines for Human Use:

XONOCOD XR

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

XONOCOD XR 5/2,5 mg prolonged release film-coated tablets

XONOCOD XR 10/5 mg prolonged release film-coated tablets

XONOCOD XR 20/10 mg prolonged release film-coated tablets

XONOCOD XR 30/15 mg prolonged release film-coated tablets

XONOCOD XR 40/20 mg prolonged release film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each XONOCOD XR 5/2,5 mg prolonged release film-coated tablet contains 5 mg oxycodone hydrochloride equivalent to 4,5 mg oxycodone and 2,5 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) equivalent to 2,25 mg naloxone.

Each XONOCOD XR 10/5 mg prolonged release film-coated tablet contains 10 mg oxycodone hydrochloride equivalent to 9 mg oxycodone and 5 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) equivalent to 4,5 mg naloxone.

Each XONOCOD XR 20/10 mg prolonged release film-coated tablet contains 20 mg oxycodone hydrochloride equivalent to 18 mg oxycodone and 10 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) equivalent to 9 mg naloxone.

Each XONOCOD XR 30/15 mg prolonged release film-coated tablet contains 30 mg oxycodone hydrochloride equivalent to 27 mg oxycodone and 15 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) equivalent to 13,5 mg naloxone.

Each XONOCOD XR 40/20 mg prolonged release film-coated tablet contains 40 mg oxycodone hydrochloride equivalent to 36 mg oxycodone and 20 mg naloxone hydrochloride (as naloxone hydrochloride dihydrate) equivalent to 18 mg naloxone.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged Release Film-coated tablet.

5/2,5 mg tablets are: White, round, biconvex, prolonged release film-coated tablets with a diameter of 4,7 mm and a height of 2,9 – 3,9 mm.

10/5 mg tablets are: Pink, oblong, biconvex, prolonged release film-coated tablets 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.

20/10 mg tablets are: White, oblong, biconvex, prolonged release film-coated tablets 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.

30/15 mg tablets are: Yellow, oblong, biconvex, prolonged release film-coated tablets 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.

40/20 mg tablets are: Pink, oblong, biconvex prolonged release film-coated tablet with break scores on both sides 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

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

4.2 Posology and method of administration

Posology

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

XONOCOD XR is taken at the determined dosage, twice daily according to a fixed time schedule.

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

Unless otherwise prescribed, XONOCOD XR should be administered as follows:

Adults: The usual starting dose for an opioid naïve patient is 10 mg/5 mg of XONOCOD XR at 12 hourly intervals.

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

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

The maximum daily dose of XONOCOD XR is 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride.

Patients taking XONOCOD XR according to a regular time schedule may require immediate release analgesics as "rescue" medication for breakthrough pain. XONOCOD XR 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 XONOCOD XR requires upward adjustment. This adjustment should be made every 1-2 days in steps of twice daily 5 mg/2,5 mg, or where demanded 10 mg/5 mg, XONOCOD XR until a stable dose is reached.

The aim is to establish a patient-specific, twice daily dose that will maintain adequate analgesia and make use of as little rescue medication as possible for as long as pain therapy is necessary.

Children and adolescents under 18 years: The safety and efficacy of XONOCOD XR in patients below the age of 18 years of age has not been established. XONOCOD XR is not recommended for use in children and adolescents below the age of 18.

Special populations

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

Duration of use: XONOCOD XR should not be administered for longer than absolutely necessary.

If long-term pain treatment is necessary in view the nature and severity of the illness, careful and regular monitoring is required to establish whether and to what extent further treatment is necessary. When the patient no longer requires opioid therapy, it may be advisable to taper the dose gradually (see section 4.4).

Adult patients with impaired hepatic function: A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone concentrations were affected to a higher degree than oxycodone (see section 5.2). The clinical relevance of a relative high naloxone exposure in hepatic impaired patients is yet not known. Caution must be exercised when administering XONOCOD XR to patients with mild hepatic impairment (see section 4.4). In patients with moderate and severe hepatic impairment XONOCOD XR is contraindicated (see section 4.3).

Adult patients with impaired renal function: A clinical trial has shown that plasma concentrations of both oxycodone and naloxone are significantly elevated in patients with renal impairment and is contraindicated (see section 5.2 and 4.3). Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in renal impaired patients is yet not known. XONOCOD XR is contraindicated in moderate to severe renal impairment. Caution should be exercised when administering XONOCOD XR to patients with mild renal impairment (see section 4.3).

Method of administration

For oral use.

XONOCOD XR must be swallowed whole and not broken or chewed. It may be taken with or without food with sufficient liquid.

4.3 Contraindications

- XONOCOD XR is contraindicated in patients with known hypersensitivity to oxycodone hydrochloride and naloxone hydrochloride or to any of the excipients listed in section 6.1.
- Any situation where opioids are contraindicated;
- Severe respiratory depression with hypoxia and/or hypercapnoea;
- Severe chronic obstructive pulmonary disease;
- Cor pulmonale;
- Severe bronchial asthma;
- Non-opioid induced paralytic ileus;
- Moderate to severe hepatic impairment;
- Moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Respiratory depression

The major risk of opioid excess is respiratory depression.

Caution must be exercised when administering XONOCOD XR to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, patients with sleep apnoea, myxoedema, hypothyroidism, Addison's disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions. Caution is advised in patients taking monoamine Oxidase (MAO) inhibitors or central nervous system (CNS) depressants.

Risk from concomitant use of sedative medicines such as benzodiazepines or related Medicines: Concomitant use of opioids, including oxycodone

hydrochloride and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe XONOCOD XR 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 monitored 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).

Hepatic or renal impairment

Caution must also be exercised when administering XONOCOD XR to patients with mild hepatic or renal impairment.

Diarrhoea

Diarrhoea may be considered as a possible effect of naloxone.

Long-term opioid treatment

In patients under long-term opioid treatment with higher doses of opioids, the switch to XONOCOD XR can initially provoke withdrawal symptoms. Such patients may require specific attention.

XONOCOD XR is not suitable for the treatment of withdrawal symptoms.

During long-term administration, the patient may develop tolerance to XONOCOD XR and require higher doses to maintain the desired effect. Chronic administration of XONOCOD XR tablets may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy 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). There is no clinical experience with XONOCOD XR in the long-term treatment of Restless legs syndrome (RLS) beyond 1 year (see section 4.2).

Psychological dependence (addiction)

There is potential for development of psychological dependence (addiction) to opioid analgesics, including XONOCOD XR.

XONOCOD XR should be used with particular care in patients with a history of alcohol and medicine abuse. Oxycodone alone has an abuse profile similar to other strong agonist opioids.

In order not to impair the prolonged-release characteristic of the prolonged-release tablets, the prolonged-release tablets must be taken whole and must not be broken, chewed or crushed. Breaking, chewing or crushing the prolonged-release tablets for ingestion leads to a faster release of the active substances and the absorption of a possibly fatal dose of oxycodone (see section 4.9).

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 medicines in combination with XONOCOD XR (see sections 4.5 and 4.7).

Alcohol

Concomitant use of alcohol and XONOCOD XR may increase the undesirable effects of XONOCOD XR, 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 these tablets in this population is not recommended.

Surgery

XONOCOD XR tablets are 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 XONOCOD XR tablets depends on a careful risk-benefit assessment for each individual patient.

Abuse

Any abuse of XONOCOD XR tablets by drug addicts is strongly discouraged.

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists, such as heroin, morphine, or methadone, XONOCOD XR are 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).

XONOCOD XR is 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.

Hormonal changes

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.

Doping

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

Paediatric population

Studies have not been performed on the safety and efficacy of XONOCOD XR 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.

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of opioids with sedative medicines such as benzodiazepines or related Medicines increases the risk of sedation, respiratory

depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Medicines which depress the CNS include, but are not limited to: other opioids, gabapentinoids such as pregabalin, anxiolytics, hypnotics and sedatives (including benzodiazepines), anti-depressants, antipsychotics, anti-histamines and anti-emetics.

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 XONOCOD XR; 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 such as warfarin are co-administered.

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 medicines or dietary elements. XONOCOD XR 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 XONOCOD XR 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 medicine, resulting in a decrease in oxycodone plasma concentrations.

Caution is advised and further titration may be necessary to reach an adequate level of pain control.

Theoretically, medicines 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

XONOCOD XR is not recommended for use in pregnancy or during labour.

Both oxycodone and naloxone pass into the placenta.

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

Breastfeeding

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

Fertility

There are no data with respect to fertility.

4.7 Effects on ability to drive and use machines

XONOCOD XR can have an influence on the ability to drive and use machines. This is particularly likely at the beginning of treatment, after dose increase or product rotation and if XONOCOD XR tablets are combined with other CNS depressant medicines. Patients stabilised on a specific dosage will not

necessarily be restricted. Therefore, patients should consult with their medical practitioner as to whether driving or the use of machinery is permitted.

Patients being treated with XONOCOD XR 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).

XONOCOD XR can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

a) **Summary of the safety profile**

The most commonly reported adverse reactions in patients taking Oxycodone and Naloxone. {Note: Side effects have been amended to align with IPI: Very common/Common ≡ Frequent; Uncommon/Rare/Very rare ≡ Less Frequent & Unknown is unknown frequency

b) **Tabulated summary of adverse reactions**

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders	Decreased appetite up to loss of appetite		
Psychiatric disorders	Insomnia, restlessness	Abnormal thinking, anxiety, confusional state, depression, libido decreased, nervousness, nightmares,	

		medicine dependence. euphoric mood, hallucination.	
Nervous system disorders	Dizziness, headache, somnolence, paraesthesia	Convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), disturbance in attention, dysgeusia, speech disorder, syncope, tremor, lethargy, sedation	
Eye disorders		Visual impairment	
Ear and labyrinth disorders	Vertigo		
Cardiac disorders		Angina pectoris (in particular in patients with history of coronary artery disease), palpitations (in the context of withdrawal syndrome), tachycardia	

Vascular disorders	Hot flush, decreased blood pressure	Increased blood pressure	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, rhinorrhoea, cough, yawning, respiratory depression	
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, rash, 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	Medicine withdrawal syndrome, asthenia, fatigue, chills, feeling hot and cold.	Chest pain, malaise, pain, peripheral oedema, thirst	
Injury, poisoning and procedural complications		Injuries from accidents	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6,04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of intoxication

Depending on the history of the patient, an overdose of XONOCOD XR 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.

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 dysrhythmias may require cardiac

massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 2.9 Other Analgesics

Pharmacotherapeutic group: Analgesics; Opioids; Natural opium alkaloids

ATC Code: N02AA55

Oxycodone and naloxone have an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the CNS. Naloxone is a pure antagonist acting on all types of opioid receptors.

The absolute bioavailability of naloxone upon oral administration is < 3 %.

Naloxone antagonises the opioid receptor mediated oxycodone effect.

Opioids can influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase of prolactin in the serum and a reduced level of cortisol and testosterone in the plasma. Clinical symptoms may occur because of these hormone changes.

5.2 Pharmacokinetic properties

Oxycodone

Absorption

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

Distribution

Following absorption, oxycodone is distributed throughout the entire body.

Approximately 45 % is bound to plasma protein. Oxycodone crosses the placenta and may be detected in breast milk.

Biotransformation

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

Elimination

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

Naloxone hydrochloride

Absorption

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

Distribution

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

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, 6-β-Naloxol and its glucuronide.

Oxycodone hydrochloride/naloxone hydrochloride combination

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

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

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

Pharmacokinetics in special population

Elderly patients

Oxycodone: For AUC_T of oxycodone, on average there was an increase to 118 % (90 % C.I.: 103, 135), for elderly compared with younger volunteers. For C_{max} of oxycodone, on average there was an increase to 114 % (90 % C.I.: 102, 127). For C_{min} of oxycodone, on average there was an increase to 128 % (90 % C.I.: 107, 152).

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

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

Patients with impaired renal function:

Oxycodone: For AUC_{INF} of oxycodone, on average there was an increase to 153 % (90 % C.I.: 130, 182), 166 % (90 % C.I.: 140, 196) and 224 % (90 % C.I.: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 110 % (90 % C.I.: 94, 129), 135 % (90 % C.I.: 115, 159) and 167 % (90 % C.I.: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2Z}$ of oxycodone, on

average there was an increase to 149 %, 123 % and 142 % for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone: For AUC_t of naloxone, on average there was an increase to 2850 % (90 % C.I.: 369, 22042), 3910 % (90 % C.I.: 506, 30243) and 7612 % (90 % C.I.: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 1076 % (90 % C.I.: 154, 7502), 858 % (90 % C.I.: 123, 5981) and 1675 % (90 % C.I.: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available $t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values. The ratios may have been influenced by the inability to fully characterise the naloxone plasma profiles for the healthy subjects.

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

Patients with impaired hepatic function:

Oxycodone: For AUC_{INF} of oxycodone, on average there was an increase to 143 % (90 %u 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone*

Kollidon® SR, consisting of: Polyvinyl acetate (80 %)

Povidone (19 %)

Sodium lauryl sulphate (0,8 %)

Silica, colloidal anh. (0,2 %)

Cellulose, microcrystalline

Silica, colloidal anhydrous

Magnesium stearate

Film-coat:

Opadry® II White,

consisting of:

Polyvinyl alcohol (40 %)

Talc (14,8 %)

Titanium dioxide (E171) (25 %)

Macrogol 3350 (20,2 %)

Opadry Red (Used in 10 / 5 mg & 40 / 20 mg

Opadry® II Red,

consisting of:

Polyvinyl alcohol (40 %)

Talc (14,8 %)

Macrogol 3350 (20,2 %)

Iron oxide red (E172) (25 %)

Opadry Yellow (used in 30 mg / 15 mg)

Opadry® II Yellow,

consisting of:

Polyvinyl alcohol (40 %)

Talc (14,8 %)

Iron oxide yellow (E172) (25 %)

Macrogol 3350 (20,2 %)

Purified water

*Povidone is used in 5/2,5 mg & 10/5 mg Tablets

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years

Bottles: 3 years

In-use shelf life: 3 months after first opening

6.4 Special precautions for storage

HDPE bottle: store at or below 30 °C.

Blister pack: store at or below 25 °C.

6.5 Nature and contents of container

The tablets are packaged in and blister pack manufactured from PVC-PE-PVDC bottom film and reinforced aluminium lid foil ensuring child-resistance in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 90, 98 or 100 tablets in carton boxes. Not all pack sizes may be marketed.

High density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) twist-off caps pack of 50, 100 and 250 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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2193

South Africa

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8. REGISTRATION NUMBER(S)

XONOCOD XR 5/2,5 mg: 53/2.9/0745

XONOCOD XR 10/5 mg: 53/2.9/0746

XONOCOD XR 20/10 mg: 53/2.9/0747

XONOCOD XR 30/15 mg: 53/2.9/0748

XONOCOD XR 40/20 mg: 53/2.9/0749

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2023

10. DATE OF REVISION OF THE TEXT