Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxycodone Hydrochloride Teva 20 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20.0 mg oxycodone hydrochloride corresponding to 17.93 mg oxycodone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (capsule)

Hard capsules, 14.4 mm in length, with a light pink body marked with ‘20’ and a brown cap marked with ‘OXY’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology

The dosage depends on the intensity of pain and the patient’s individual susceptibility to the treatment. The following general dose recommendations apply:

Adults and adolescents over 12 years of age

Dose initiation
In general, the initial dose for opioid naïve patients is 5 mg oxycodone hydrochloride given at intervals of 6 hours. Patients already receiving opioids may start treatment with higher doses taking into account their experience with former opioid therapies.

Patients receiving oral morphine before oxycodone therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It should be noted that this is a guide to the dose of oxycodone hydrochloride capsules required. Inter−patient variability requires that each patient is carefully titrated to the appropriate dose.

Dose adjustment
Increasing severity of pain will require an increased dose of Oxycodone Hydrochloride Teva. The dose should be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. In doing so, the dosing interval may be reduced to 4 hours. The correct dose for any individual patient is that which controls the pain and is well tolerated throughout the dosing period.

The majority of patients will not require a daily dose greater than 400 mg. However, a few patients may require higher doses.

In patients receiving a prolonged−release formulation of oxycodone, Oxycodone Hydrochloride Teva may be used to control breakthrough pain. The dose should be adjusted according to the patient´s need but as a general rule the single

dose should amount to 1/8 to 1/6 of the daily dose of the prolonged−release formulation. The rescue medication should not be used more frequently than every 6 hours.

Method of administration
For oral use.
Oxycodone Hydrochloride Teva should be administered using a fixed schedule at the dose determined but not more often than every 4 to 6 hours.
The capsules may be taken with or without food with a sufficient amount of liquid.

The medicinal product should not be taken with alcoholic beverages.

Duration of administration
Oxycodone Hydrochloride Teva capsules should not be taken longer than necessary. If long−term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued. If opioid therapy is no longer indicated it may be advisable to reduce the daily dose gradually in order to prevent symptoms of a withdrawal syndrome.

Paediatric population
Oxycodone Hydrochloride Teva is not recommended for children under 12 years of age as the safety and efficacy has not been established.

Elderly patients
The lowest dose should be administered with careful titration to pain control.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Risk patients
Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve.
Therefore the lowest recommended dose, i.e. 5 mg, may not be suitable as a starting dose.
Dose titration should be performed in accordance with the individual clinical situation and using the appropriate formulation as available.

4.3 Contraindications

- Hypersensitivity to the active substance 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.
- Paralytic ileus.
- Acute abdomen, delayed gastric emptying.

Oxycodone must not be used in any situation where opioids are contraindicated.

4.4 Special warnings and precautions for use

Caution is required in elderly or debilitated patients, in patients with severe impairment of lung, liver or kidney function, myxoedema, hypothyroidism, Addison’s disease (adrenal insufficiency), intoxication psychosis (e.g. alcohol), prostatic hypertrophy, adrenocortical insufficiency, alcoholism, known opioid dependence, delirium tremens, pancreatitis, diseases of the biliary tract, inflammatory bowel disorders, biliary or ureteric colic, hypotension, hypovolaemia, conditions with increased brain pressure such as head injury, disturbances of

circulatory regulation, epilepsy or seizure tendency and in patients taking MAO inhibitors.

As with all opioid preparations, oxycodone products should be used with caution following abdominal surgery as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function.

Patients with severe hepatic impairment should be closely monitored.

Respiratory depression is the most significant risk induced by opioids and is most likely to occur in elderly or debilitated patients. The respiratory depressant effect of oxycodone can lead to increased carbon dioxide concentrations in blood and hence in cerebrospinal fluid. In predisposed patients opioids can cause severe decrease in blood pressure.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product [preparation] may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur, particularly in high doses. An oxycodone dose reduction or change to an alternative opioid may be required.

Oxycodone Hydrochloride Teva capsules have a primary dependence potential. Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. However, when used as directed in patients with chronic pain the risk of developing physical or psychological dependence is markedly reduced or needs to be assessed in a differentiated manner. There are no data available on the actual incidence of psychological dependence in chronic pain patients. In patients with a history of alcohol and drug abuse the medicinal product must be prescribed with special care.

Oxycodone Hydrochloride Teva capsules should be used with caution pre-operatively and within the first 12-24 hours post-operatively.
In case of abusive parenteral venous injection the capsule content (especially talc) may lead to serious, potentially fatal events.

The capsules must not be taken together with alcoholic beverages, since alcoholic drinks enhance the impairment of alertness and reactivity and may increase the incidence of undesirable effects (e.g. somnolence, respiratory depression).

Paediatric population
Oxycodone has not been studied in children younger than 12 years of age. The safety and efficacy of the capsules have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as other opioids, sedatives, hypnotics, anti-depressants, phenothiazines and neuroleptic drugs. MAO-inhibitors are known to interact with narcotic analgesics. MAO-inhibitors cause CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).
Alcohol may enhance the pharmacodynamic effects of oxycodone; concomitant use should be avoided.

Anticholinergics (e.g. neuroleptics, antihistamines, antiemetics, antiparkinson medicinal products) can enhance the anticholinergic undesirable effects of oxycodone (such as constipation, dry mouth or micturition disorders).

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.
Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account. The potential effect of oxycodone on cytochrome P450-enzymes has not been studied in vitro or in vivo.

Clinically relevant changes in International Normalised Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co−applied with oxycodone hydrochloride capsules.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy
There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone.

Breastfeeding
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.
With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

4.8 Undesirable effects

Oxycodone can cause respiratory depression, miosis, bronchial spasms and spasms of the smooth muscles and can suppress the cough reflex.

The adverse reactions considered at least possibly related to treatment are listed below by system organ class and absolute frequency.

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
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
Rare Very	<1/10,000
Frequency unknown	Cannot be estimated from the available data

Infections and infestations
Rare: Herpes simplex.

Blood and lymphatic system disorders
Rare: Lymphadenopathy.

Immune system disorders
Uncommon: Hypersensitivity reactions.
Frequency unknown: Anaphylactic responses.

Endocrine disorders:
Uncommon: Syndrome of inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders
Common: Anorexia; loss of appetite.
Uncommon: Dehydration
Rare: Increased appetite.

Psychiatric disorders
Common: Various psychological adverse reactions including changes in mood (e.g. anxiety, depression), changes in activity (mostly suppression sometimes associated with lethargy, occasionally increase with nervousness and insomnia) and changes in cognitive performance (abnormal thinking, confusional state).
Uncommon: Change in perception such as depersonalisation, hallucinations; decreased libido. Agitation; affect lability; euphoric mood; drug dependence (see section 4.4)
Frequency unknown: aggression

Nervous system disorders
Very common: Somnolence; dizziness; headache.
Common: Tremor.
Uncommon: Both increased and decreased muscle tone; involuntary muscle contractions; Convulsions, in

particular in epileptic patients or patients with tendency to convulsions; hypertonia; hypoaesthesia; Speech disorder; syncope; paraesthesia; coordination disturbances; change in taste; migraine; amnesia.
Frequency unknown: hyperalgesia

Eye disorders
Uncommon: Lacrimation disorder; miosis; visual impairment.

Ear and labyrinth disorders
Uncommon: Hyperacousis; vertigo.

Cardiac disorders
Uncommon: Supraventricular tachycardia; palpitations (in the context of withdrawal syndrome).

Vascular disorders
Uncommon: Vasodilatation.
Rare: Hypotension; orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders
Common: bronchospasm; dyspnoea; hiccups.
Uncommon: Respiratory depression; cough; pharyngitis; rhinitis; voice changes.

Gastrointestinal disorders
Very common: Constipation; nausea; vomiting.
Common: Dry mouth; abdominal pain; diarrhoea; dyspepsia.
Uncommon: Dysphagia; oral ulcers; gingivitis; stomatitis; flatulence; eructation; ileus.
Rare: Gum bleeding; tarry stools; tooth staining and damage.
Frequency unknown: dental caries.

Hepato-biliary disorders
Uncommon: Increased hepatic enzymes.
Frequency unknown: Cholestasis; biliary colic

Skin and subcutaneous tissue disorders
Very common: Pruritus.
Common: Skin eruptions including rash; hyperhidrosis.
Uncommon: Dry skin.
Rare: Urticaria; photosensitivity.
Very rare: exfoliative dermatitis.

Musculoskeletal and connective tissue disorders
Rare: Muscle spasm.

Renal and urinary disorders
Common: Increased urge to urinate.
Uncommon: Urinary retention.
Rare: Haematuria.

Reproductive system and breast disorders
Uncommon: Erectile dysfunction.
Frequency unknown: Amenorrhoea.

General disorders and administration site conditions
Common: Asthenic conditions.
Uncommon: Pain (e.g. chest pain); chills; oedema; peripheral oedema; malaise; physical dependence with withdrawal syndrome; drug tolerance; thirst.
Rare: Weight changes (increase or decrease); cellulitis.

Injury, poisoning and procedural complications
Uncommon: Accidental injuries.

Counteractive measures:
As constipation is a very common side effect it may be helpful to instruct the patient that this may be prevented by a fiber enriched diet and increased intake of fluids.
For nausea and vomiting, prescribing antiemetics may be considered.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdose
Miosis, respiratory depression, somnolence, reduced skeletal muscle tone and drop in blood pressure. In severe cases circulatory collapse, stupor, coma, bradycardia and non−cardiogenic lung oedema, hypotension and death may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy of overdose
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the event of overdosing intravenous administration of an opiate antagonist (e.g. 0.4−2 mg intravenous naloxone) may be indicated. Administration of single doses must be repeated depending on the clinical situation at intervals of 2 to 3 minutes. Intravenous infusion of 2 mg of naloxone in 500 ml isotonic saline or 5% dextrose solution (corresponding to 0.004 mg naloxone/ml) is possible. The rate of infusion should be adjusted to the previous bolus injections and the response of the patient.

Gastric lavage can be taken into consideration. Consider activated charcoal (50 g for adults, 10−15 g for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected. It may be reasonable to assume that late administration of activated charcoal may be beneficial for prolonged release preparations; however there is no evidence to support this.

For speeding up the passage a suitable laxative (e.g. a PEG based solution) may be useful.

Supportive measures (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory shock. Upon cardiac arrest or cardiac arrhythmias cardiac massage or defibrillation may be indicated. If necessary, assisted ventilation as well as maintenance of water and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC−Code: N02AA05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic and sedative.

5.2 Pharmacokinetic properties

Absorption:
The absolute bioavailability of oxycodone is 60−87% following oral administration and the peak plasma concentration is achieved after approximately 1 to 1.5 hours.

Distribution:
At steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg and plasma protein binding to 38−45%.

Biotransformation:
Oxycodone is metabolised in the intestine and liver via the P450 cytochrome system to noroxycodone (CYP3A4) and oxymorphone (CYP2D6) as well as to several glucuronide conjugates. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination:
At steady state, the plasma elimination half−life amounts to approximately 3 hours. Oxycodone and its metabolites are excreted via urine. Faecal excretion has not been studied.

Linearity/non−linearity:
After administration of the capsule formulation of oxycodone hydrochloride the plasma concentration increases linear over the dose range of 5 to 20 mg.

5.3 Preclinical safety data

Oyxcodone 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.

Long-term carcinogenicity studies were not performed.
Oxycodone shows 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 to humans at therapeutic concentrations may be ruled out with adequate certainty.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Microcrystalline cellulose
Magnesium stearate

Capsule shell:
Gelatine
Sodium laurilsulfate
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

Indigotine (E132)

Printing ink:
Shellac
Propylene glycol
Ammonia solution (for pH-adjustment)
Iron oxide black (E172)
Potassium hydroxide (for pH−adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel-off blister packs (PVC/PVdC/Alu/PET/paper).
Pack sizes:
20, 28, 30, 50, 56, and 100 capsules

Push-through blister packs (PVC/PVdC/Alu).
Pack sizes:
20, 28, 30, 50, 56, and 100 capsules

HDPE containers with child resistant LDPE or PP caps.
Pack sizes: 98, 100 and 250 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Instructions for use of peel-off blisters:
1. Do not push the capsule directly out of the pocket
2. Separate one blister cell from the strip at the perforations
3. Carefully peel off the backing to open the pocket

Instruction for use of HDPE containers with child resistant LDPE or PP caps:
Push down and turn to open.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/211/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th February 2015

10 DATE OF REVISION OF THE TEXT

October 2015