Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oximel 20mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 20 mg oxycodone hydrochloride corresponding to 17.9 mg oxycodone.
Excipient with known effect:
Each prolonged-release tablet contains 46 mg lactose (as monohydrate).

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Light pink, round, biconvex, prolonged-release tablets with a diameter of 6.9 – 7.3 mm and a height of 3.5 – 4.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe pain, which can be adequately managed only with opioid analgesics.
Oximel is indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

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

Adults and adolescents 12 years of age and older
Dose titration and adjustment
In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg oxycodone hydrochloride to minimize the incidence of adverse reactions. Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies. For doses not realizable/practicable with this strength other strengths of this medicinal product are available.

According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Oxycodone hydrochloride after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Some patients who take Oxycodone hydrochloride following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Oxycodone hydrochloride is not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Oxycodone hydrochloride. Use of the rescue medication more than twice daily indicates that the dose of Oxycodone hydrochloride needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.

Following a dose increase from 10 mg to 20 mg taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient-specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as

pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non-malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individually balancing efficacy with the tolerance and risk of undesirable effects.

Duration of treatment

Oximel 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.

Discontinuation of treatment

When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Elderly patients

Elderly patients without clinical manifestation of impaired liver and/or kidney function usually do not require dose adjustments.

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 half the recommended adult dose if they are opioid naïve.
Therefore the lowest recommended dosage, i.e. 10 mg, may not be suitable as a starting dose.
Dose titration should be performed in accordance with the individual clinical situation.

Children under 12 years of age

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

Method of administration

For oral use.

Oximel should be taken twice daily based on a fixed schedule at the dosage determined.
The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Oximel must be swallowed whole, not chewed divided or crushed. Taking chewed, divided or crushed Oximel tablets may lead to a rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone hydrochloride should not be taken with alcoholic beverages.

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 elevated carbon dioxide levels in the blood (hypercapnia).
- Severe chronic obstructive pulmonary disease
- Cor pulmonale
- Severe bronchial asthma
- Paralytic ileus
- Acute abdomen, delayed gastic emptying

4.4 Special warnings and precautions for use

Respiratory and cardiac depression

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.

Tolerance and dependence

Long-term use of Oximel can cause the development of tolerance which leads to the use of higher doses in order to achieve the desired analgesic effect. There is a cross-tolerance to other opioids. Chronic use of Oximel can cause physical dependence. Withdrawal symptoms may occur following abrupt discontinuation of therapy.

If therapy with oxycodone is no longer required it may be advisable to reduce the daily dose gradually in order to avoid the occurrence of a withdrawal syndrome.

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.

Oximel has a primary dependence potential. 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.

Abuse

In case of abusive parenteral venous injection the tablet excipients (especially talc) may lead to necrosis of the local tissue, granulomas of the lung or other serious, potentially fatal events.
To avoid damage to the controlled release properties of the tablets the prolonged release tablets must be swallowed whole, not chewed, divided or crushed. The administration of chewed, divided or crushed prolonged-release tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Alcohol

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

Special patient groups

Caution is required in elderly or debilitated patients, in patients with severe impairment of lung, hepatic or renal function, myxoedema, hypothyroidism, Addison’s disease (adrenal insufficiency), intoxication psychosis (e.g. alcohol), prostatic hypertrophy, adrenocortical insufficiency, alcoholism, known opioid dependence, delirium tremens,

pancreatitis, disease of the biliary tract, biliary or ureteric colic, inflammatory bowel disorders, conditions with increased brain pressure, disturbances of circulatory regulation, epilepsy or seizure tendency and in patients taking MAO inhibitors within the last two weeks. Patients with severe hepatic impairment should be closely monitored.

Surgical procedures

Special care should be taken when oxycodone is applied to patients undergoing bowel-surgery. Opioids should only be administered post-operatively when the bowel function has been restored.

The safety of Oximel used pre-operatively has not been established.

Oximel is not recommended for pre-operative use or within the first 12 – 24 hours post operatively.

Paediatric population

The safety and efficacy of Oximel in children younger than 12 years of age have not been established. Oxycodone hydrochloride should not be used in children younger than 12 years of age because of safety and efficacy concerns.

Anti-doping warning

Athletes must be aware that this medicine may cause a positive reaction to ‘anti-doping’ tests. Use of Oximel as a doping agent may become a health hazard.

Excipient

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system depressants (e.g. sedatives, hypnotics, phenothiazines, neuroleptics, anaesthetics, antidepressants, muscle relaxants) and other opioids or alcohol can enhance the adverse reactions of oxycodone, in particular respiratory depression.
MAO inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis (see section 4.4). Oximel 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).

Oxycodone is metabolised mainly by cytochrome P450 3A4, with a contribution from CYP2D6.
The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. 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.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azolantifungals (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

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account.
Clinically relevant changes in International Normalised Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-applied with oxycodone.
There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other drugs.
Alcohol may enhance the pharmacodynamic effects of Oximel concomitant use should be avoided.

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.

Breast-feeding
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

At the beginning of therapy and after dose adjustment, oxycodone hydrochloride can have major influence on the ability to drive and use machines. Alertness and reactivity can be impaired to such an extent that the ability to drive and operate machinery is affected or ceases altogether.

With stable therapy, a general ban on driving a vehicle is not necessary. In these circumstances oxycodone hydrochloride has minor influence on the ability to drive and use machines.

The treating physician must assess the individual situation.

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

	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)
Blood and lymphatic system disorders:				Lymphadeno-pathy.	
Immune system disorders:			Hypersen-sitivity.		
Endocrine disorders:			Syndrome of inappropriate antidiuretic hormone secretion.		
Metabolism and nutrition disorders:		Anorexia; decreased appetite.	Dehydration.		
Psychiatric disorders:		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, confusion, isolated cases of speech disorders).	Change in perception such as depersonali-sation; hallucinations; affected lability; hyperacousis; euphoric mood; agitation; decreased libido; drug dependence (see section 4.4).		
Nervous system disorders:	Somnolence; dizziness; headache.	Asthenia; tremor.	Both increased and decreased muscle tone; amnesia; convulsion; hypertonia;	Seizures, in particular in epileptic patients or patients with tendency to convulsions;	

			involuntary muscle contractions; hypoaesthesia; speech disorder; syncope; paraesthesia; dysgeusia; coordination disturbances.	muscle spasm.	
Eye disorders:			Lacrimation disorder; visual impairment; miosis		
Ear and labyrinth disorders:			Vertigo, tinnitus		
Cardiac disorders:			Supraventri-cular tachycardia, palpitations (in context of withdrawal syndrome).		
Vascular disorders:			Vasodilatation	Hypotension; orthostatic hypotension.	
Respiratory, thoracic and mediastinal disorders:		Dyspnoea, bronchospasm	Respiratory depression; increased coughing; pharyngitis; rhinitis; voice changes.		
Gastrointestinal disorders:	Constipation; nausea; vomiting.	Dry mouth, rarely accompanied by thirst and difficulty swallowing; gastrointesti-nal disorders such as abdominal pain; diarrhoea; dyspepsia.	Oral ulcers; gingivitis; stomatitis; flatulence; eructation; dysphagia; ileus.	Gum bleeding; increased appetite; tarry stool; tooth staining and damage.	
Hepatobiliary disorders:			Increased hepatic enzymes.		
Skin and subcutaneous tissue disorders:	Pruritus	Skin eruptions including rash; hyperhidrosis;	Dry skin.	Herpes simplex, urticaria.	

		in rare cases increased photosensi-tivety; in isolated cases urticaria or exfoliative dermatitis.			
Renal and urinary disorders:		Micturition disturbances (increased urge to urinate).	Urinary retention.		
Reproductive system and breast disorders:			Erectil dysfunction, impotence.		
General disorders and administration site conditions:		Asthenic conditions.	Accidental injuries; pain (e.g. chest pain); malaise; oedema; peripheral oedema; migraine; physical dependence with withdrawal symptoms; drug tolerance; allergic reactions; chills; thirst.	Weight changes (increase or decrease); cellulitis.	

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 and intoxication:
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 may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy of intoxications:
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 sodium chloride 9 mg/ml (0.9%) solution for injection 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.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Naloxone should be administered cautiously to patients who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

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: Analgesics; Opioids; Natural opium alkaloids
ATC-Code: N02A A05
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. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

Other pharmacological effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semi-synthetic opioid, has immunological effects similar to morphine is unknown.

5.2 Pharmacokinetic properties

Absorption:
The relative bioavailability of Oximel is comparable to that of rapid release oxycodone with maximum plasma concentrations being achieved after approximately 3 hours after intake of the prolonged-release tablets compared to 1 to 1.5 hours. Peak plasma concentrations and oscillations of the concentrations of oxycodone from the prolonged-release and rapid-release formulations are comparable when given at the same daily dose at intervals of 12 and 6 hours, respectively.

The tablets must not be crushed, divided, or chewed as this leads to rapid oxycodone release and absorption of a potentially fatal dose of oxycodone due to the damage of the prolonged release properties.

Distribution:
The absolute bioavailability of oxycodone is approximately two thirds relative to parenteral administration.. In steady state, the volume of distribution of oxycodone amounts to 2.6 l/kg plasma protein binding to 38-45%; the elimination half-life to 4 to 6 hours and plasma clearance to 0.8 l/min. The elimination half-life of oxycodone from prolonged-release tablets is 4-5 hours with steady state values being achieved after a mean of 1 day.

Metabolism:
Oxycodone is metabolized in the intestine and liver via the P450 cytochrome system to noroxycodone and

oxymorphone as well as to several glucuronide conjugates. In vitro studies suggest that therapeutic doses of cimetidine probably have no relevant effect on the formation of noroxycodone. In man, quinidine reduces the production of oxymorphone while the pharmacodynamic properties of oxycodone remain largely unaffected. The contribution of the metabolites to the overall pharmacodynamic effect is irrelevant.

Elimination:
Oxycodone and its metabolites are excreted via urine and faeces. Oxycodone crosses the placenta and is found in breast milk.

Linearity/non-linearity:
Across the 5 - 80 mg dose range of prolonged release oxycodone tablets linearity of plasma concentrations was demonstrated in terms of rate and extent of absorption.

5.3 Preclinical safety data

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.
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

Tablet Core:
Lactose monohydrate
Ammonio Methacrylate Copolymer (type B)
Povidone (K29/32)
Talc
Triacetin
Stearyl alcohol
Magnesium stearate

Tablets coating:
Hypromellose
Talc
Macrogol 400
Titanium dioxide (E171)
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child resistant PVC/PVdC-Aluminium perforated unit dose blisters with 10x1, 14x1, 20x1, 25x1, 28x1, 30x1, 40x1, 50x1, 56x1, 60x1, 98x1 and 100x1 prolonged-release tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.,
Waterford Road,
Clonmel,
Co. Tipperary,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/264/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th September 2014

10 DATE OF REVISION OF THE TEXT

August 2015