1. Trade Name of the Medicinal Product

OxyContin® 5 mg, 10 mg, 20 mg, 40 mg, 80 mg film-coated, prolonged release tablets ▼

2. Qualitative and Quantitative Composition

5 mg tablet contains 4.5 mg of oxycodone as 5 mg of oxycodone hydrochloride.
10 mg tablet contains 9.0 mg of oxycodone as 10 mg of oxycodone hydrochloride.
20 mg tablet contains 18.0 mg of oxycodone as 20 mg of oxycodone hydrochloride.
40 mg tablet contains 36.0 mg of oxycodone as 40 mg of oxycodone hydrochloride.
80 mg tablet contains 72.0 mg of oxycodone as 80 mg of oxycodone hydrochloride.
For excipients see section 6.1.

3. Pharmaceutical Form

Film coated, prolonged release, round, convex tablet.
The 5 mg tablets are light blue, marked OC on one side and 5 on the other.
The 10 mg tablets are white, marked OC on one side and 10 on the other.
The 20 mg tablets are pink, marked OC on one side and 20 on the other.
The 40 mg tablets are yellow, marked OC on one side and 40 on the other.
The 80 mg tablets are green, marked OC on one side and 80 on the other.

Clinical Particulars

4.1. Therapeutic Indications

For the treatment of moderate to severe pain in patients with cancer and post-operative pain.
For the treatment of severe pain requiring the use of a strong opioid.

4.2. Posology and Method of Administration

OxyContin tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

OxyContin is not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of ***OxyContin*** tablets using the 5 mg, 10 mg, 20 mg, 40 mg or 80 mg tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary increases should be made, where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of ***OxyContin*** tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been recorded.

Patients receiving oral morphine before ***OxyContin*** 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 must be emphasised that this is a guide to the dose of ***OxyContin*** tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Children under 18 years:
There were no studies in patients below 18 years of age, therefore ***OxyContin*** should not be used in patients under 18 years.

Adults with mild to moderate renal impairment and mild hepatic impairment:
The plasma concentration in this population may be increased. Therefore dose initiation should follow a conservative approach. Patients should be started on ***OxyContin*** 5 mg 12-hourly or ***OxyNorm*** liquid 2.5 mg 6-hourly and titrated to pain relief as described above.

Use in non-malignant pain:
Opioids are not first line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

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.

4.3. Contra-indications

Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity or in any situation where opioids are contraindicated, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance <10 ml/min), chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Pregnancy.

4.4. Special Warnings and Precautions for Use

The major risk of opioid excess is respiratory depression. As with all narcotics, a reduction in dosage may be advisable in hypothyroidism. Use with caution in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychosis, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, chronic renal and hepatic disease or severe pulmonary disease, and debilitated, elderly and infirm patients. ***OxyContin*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***OxyContin*** tablets should be discontinued immediately. As with all opioid preparations, patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive ***OxyContin*** tablets for 24 hours before surgery. If further treatment with ***OxyContin*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement. ***OxyContin*** 80 mg should not be used in patients not previously exposed to opioids. This tablet strength may cause fatal respiratory depression when administered to opioid naïve patients.

As with all opioid preparations, ***OxyContin*** tablets 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.

For appropriate patients who suffer with chronic non-malignant pain, opioids should be used as part of a comprehensive treatment programme involving other medications and treatment modalities. A crucial part of the assessment of a patient with chronic non-malignant pain is the patient's addiction and substance abuse history. ***OxyContin*** tablets should be used with particular care in patients with a history of alcohol and drug abuse.

If opioid treatment is considered appropriate for the patient , then the main aim of treatment is not to minimise the dose of opioid but rather to achieve a dose which provides adequate pain relief with a minimum of side effects. There must be frequent contact between physician and patient so that dosage adjustments can be made. It is strongly recommended that the physician defines treatment outcomes in accordance with pain management guidelines. The physician and patient can then agree to discontinue treatment if these objectives are not met.

OxyContin has an abuse liability similar to other strong opioids and should be used with caution in opioid dependent patients, or if the doctor or pharmacist is concerned about the risk of misuse. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

OxyContin tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed ***OxyContin*** tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see Section 4.9). Abuse of the tablets by parenteral administration can be expected to result in other serious adverse events, such as local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, which may be fatal.

4.5. Interactions with other Medicaments and other forms of Interaction

OxyContin, like other opioids, potentiates the effects of tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, alcohol, other opioids, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hypertensive or hypotensive crisis. Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone C_{max} by 11%, AUC by 13%, and $t_{½}$ elim. by 14%. Also an increase in noroxycodone level was observed, (C_{max} by 50%; AUC by 85%, and $t_{½}$ elim. by 42%). The pharmacodynamic effects of oxycodone were not altered. This interaction may be observed for other potent inhibitors of cytochrome P450-2D6 enzyme. Cimetidine and inhibitors of cytochrome P450-3A such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone.

4.6. Pregnancy and Lactation

OxyContin tablets are not recommended for use in pregnancy.

Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. ***OxyContin*** tablets should, therefore, not be used in breast-feeding mothers.

4.7. Effects on Ability to Drive and Use Machines

Oxycodone may modify patients' reactions to a varying extent depending on the dosage and individual susceptibility. Therefore patients should not drive or operate machinery if affected.

4.8. Undesirable Effects

Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur (see *Tolerance and Dependence*, below). Constipation may be prevented with an appropriate laxative. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic.

Common (incidence of ≥1%) and uncommon (incidence of ≤1%) adverse drug reactions are listed in the table below.

Body System	Common	Uncommon
Gastrointestinal	Constipation Nausea Vomiting Dry mouth Anorexia Dyspepsia Abdominal pain Diarrhoea	Biliary spasm Dysphagia Eructation Flatulence Gastrointestinal disorders Ileus Taste perversion Gastritis Hiccups
Central Nervous System	Headache Confusion Asthenia Faintness Dizziness Sedation Anxiety Abnormal dreams Nervousness Insomnia Thought abnormalities Drowsiness Twitching	Vertigo Hallucinations Hypertonia Disorientation Mood changes Restlessness Agitation Depression Tremor Withdrawal syndrome Amnesia Hypoaesthesia Hypotonia Malaise Paraesthesia Speech disorder Euphoria Dysphoria Seizure Vision abnormalities
Genitourinary		Urinary retention Ureteric spasm Impotence Amenorrhoea Decreased libido
Cardiovascular	Orthostatic hypotension	Palpitations Supraventricular tachycardia

		Hypotension Syncope Vasodilation
Metabolic and Nutritional		Dehydration Oedema Peripheral oedema Thirst
Respiratory	Bronchospasm Dyspnoea Decreased cough reflex	Overdose may produce respiratory depression
Dermatological	Rash Pruritus	Dry skin Exfoliative dermatitis Urticaria
General	Sweating Chills	Facial flushing Miosis Muscular rigidity Allergic reaction Fever Anaphylaxis

Tolerance and Dependence:
The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of ***OxyContin*** tablets 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. The opioid abstinence or withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate or heart rate.

The development of psychological dependence (addiction) to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of psychological dependence (addiction) in chronic pain patients.

OxyContin tablets should be used with particular care in patients with a history of alcohol and drug abuse.

4.9. Overdose

Signs of oxycodone toxicity and overdosage are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases.

Treatment of oxycodone overdosage: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. ***OxyContin*** tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and the management of oxycodone overdosage should be modified accordingly.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage. Naloxone should be administered cautiously to persons 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 contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a prolonged release formulation has been taken.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

5.2. Pharmacokinetic Properties

Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration. Oxycodone has an elimination

half-life of approximately 3 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from ***OxyContin*** tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release which determines the 12 hour duration of action. The mean apparent elimination half-life of ***OxyContin*** is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from ***OxyContin*** tablets is independent of pH.

OxyContin tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from ***OxyContin*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

OxyContin tablets 5 mg, 10 mg, 20 mg, 40 mg and 80 mg are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from ***OxyContin*** tablets.

Elderly
The AUC in elderly subjects is 15% greater when compared with young subjects.

Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Patients with renal impairment
Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{½}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic impairment
Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{½}$ elimination for oxycodone increased by 2.3 hours.

5.3. Preclinical Safety Data

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 μg/ml, and in the *in vivo* bone marrow micronucleus assay in mice (at plasma levels

of up to 48 μg/ml). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/ml or greater with metabolic activation and at 400 μg/ml or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pharmaceutical Particulars

6.1. List of Excipients

Lactose monohydrate
Povidone
Ammoniomethacrylate co-polymer
Sorbic acid
Glyceryl triacetate
Stearyl alcohol
Talc
Magnesium stearate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol

In addition the tablets contain the following:

5 mg	Brilliant blue (E133)
10 mg	Hydroxypropylcellulose
20 mg and 40 mg	Polysorbate 80, iron oxide (E172).
80 mg	Hydroxypropylcellulose, iron oxide (E172), indigo carmine (E132)

6.2. Incompatibilities

None known.

6.3. Shelf Life

Three years.

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

PVC blister packs with aluminium foil backing containing 28 tablets (5 mg) or 56 tablets (10, 20, 40, 80 mg).

6.6. Instruction for Use/Handling

None.

7. Marketing Authorisation Holder

Napp Pharmaceuticals Ltd
Cambridge Science Park
Milton Road
Cambridge CB4 0GW

8. Marketing Authorisation Numbers

PL 16950/0097-0100, 0123

9. Date of First Authorisation/Renewal of Authorisation

10, 20, 40, 80 mg tablets: 5 March 1999
5 mg tablets: 21 May 2002

10. Date of (Partial) Revision of the Text

November 2003

11. Legal Category

CD (Sch 2) POM