Doctor Leaflet

1. NAME OF THE MEDICINAL PRODUCT

OxyContin*® 10, 20, 40, 80 Controlled Release Tablets *(New Formulation)
***OxyContin*® 5 Controlled Release Tablets**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OxyContin 5 contains 5 mg of oxycodone hydrochloride.
OxyContin 10 contains 10 mg of oxycodone hydrochloride.
OxyContin 20 contains 20 mg of oxycodone hydrochloride.
OxyContin 40 contains 40 mg of oxycodone hydrochloride.
OxyContin 80 contains 80 mg of oxycodone hydrochloride.

For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Controlled release tablets.

The 5 mg tablets are light blue.
The 10 mg tablets are white.
The 20 mg tablets are pink.
The 40 mg tablets are yellow.
The 80 mg tablets are green.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see 'Drug Interactions'].

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

For the relief of moderate to severe chronic pain.

4.2 Posology and method of administration

OxyContin tablets must be swallowed whole, and not broken, chewed or crushed.

OxyContin tablets should be taken one tablet at a time. Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

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.

Pediatric use
OxyContin 10, 20, 40, 80: should not be used in patients under 18 years of age.
OxyContin 5**:** Safety and effectiveness of ***OxyContin*** in pediatric patients below the age of 18 years have not been established.

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 oxycodone HCl 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 Contraindications

Hypersensitivity to any of the constituents, respiratory depression, head injury, known or suspected paralytic ileus and GI obstruction, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, cor pulmonale, severe bronchial asthma, hypercarbia, known oxycodone sensitivity or in any situation where opioids are contra-indicated, 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 the 5 mg strength. Pregnancy.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Closely monitor patients for respiratory depression when initiating therapy with OxyContin and following dose increases.

Instruct patients on proper administration of OxyContin tablets to reduce the risk

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, alcoholism, delirium tremens, chronic renal and hepatic disease or severe pulmonary disease, and debilitated, elderly patients.

The oxycodone in ***OxyContin*** may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during ***OxyContin*** therapy.

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 about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive ***OxyContin*** tablets for 12 hours prior to the intervention. If further treatment with ***OxyContin*** tablets is indicated then 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. There is potential for development of psychological dependence (addiction) to opioid analgesics, including oxycodone. ***OxyContin*** tablets, like all opioids, should be avoided in patients with a history of, or present 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.

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

OxyContin has an abuse profile similar to other strong opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders.

As with other opioids, infants who are born to dependent mothers may exhibit withdrawal symptoms and may have respiratory depression at birth.

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).

OxyContin 10, 20, 40, 80: There have been post-marketing reports of difficulty in swallowing ***OxyContin*** tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet ***OxyContin*** tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth. There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Use caution when prescribing ***OxyContin*** for patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

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

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 Interaction with other medicinal products and other forms of interaction

OxyContin, like other opioids, potentiates the effects of tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neuroleptic drugs, 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 use of ***OxyContin*** and other central nervous system (CNS) depressants including sedatives or hypnotics such as benzodiazepines, general anesthetics, phenothiazines, tranquilizers, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation or coma. Monitor patients receiving CNS depressants and ***OxyContin*** for signs of respiratory depression and hypotension. When such combined therapy is contemplated, reduce the initial dose of ***OxyContin*** and consider using a lower dose of the concomitant CNS depressant.

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

Mixed Agonist/Antagonist Opioid Analgesics (i.e., pentazocine, nalbuphine, and butorphanol) - should generally not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as ***OxyContin***. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients.

Diuretics - opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.

Anticholinergics or other medications with anticholinergic activity - when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which

may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when OxyContin is used concurrently with anticholinergic drugs.

Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements. Oxycodone doses may need to be adjusted accordingly.

Cimetidine and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., clarithromycin, erythromycin), azole-antifungal agents (e.g., ketoconazole, voriconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and cause increased clearance of the drug, resulting in a decrease in oxycodone plasma concentrations.

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.

4.6 Pregnancy and lactation

OxyContin tablets are not recommended for use in pregnancy nor during labour. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

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
Immune system disorders		Anaphylactic reaction Anaphylactoid reaction Hypersensitivity
Metabolism and nutritional disorders	Decreased appetite Anorexia	Dehydration
Psychiatric disorders	Anxiety Confusional state Insomnia Nervousness Thinking abnormal Abnormal dreams	Affect lability Agitation Drug dependence Euphoric mood Hallucination Libido decreased

Body System	Common	Uncommon
	Depression	Disorientation Mood altered Restlessness Dysphoria
Nervous system disorders	Headache Dizziness Sedation Somnolence Tremor	Amnesia Hypertonia Hypoaesthesia Hypotonia Paresthesia Speech disorder Convulsions Muscle contractions involuntary Dysgeusia Syncope Hyperalgesia
Eye disorders		Miosis Vision impairment
Ear and labyrinth disorders		Vertigo Tinnitus
Cardiac disorders		Supraventricular tachycardia
Vascular disorders		Hypotension Orthostatic hypotension Vasodilatation Facial flushing
Respiratory, thoracic and mediastinal disorders	Bronchospasm Dyspnoea Cough decreased	Respiratory depression Hiccups
Gastrointestinal disorders	Constipation Nausea Vomiting Dry mouth Dyspepsia Abdominal Pain Diarrhoea	Dental caries Dysphagia Eructation Flatulence Ileus Gastritis
Hepato-biliary disorders		Biliary colic Cholestasis Hepatic enzyme increased
Skin and subcutaneous tissue disorders	Hyperhidrosis Pruritus Rash	Dry skin Exfoliative dermatitis
Musculoskeletal and connective tissue disorders		Muscular rigidity
Renal and urinary disorders		Urinary retention Ureteral spasm
Reproductive system and breast disorders		Amenorrhoea Erectile dysfunction

Body System	Common	Uncommon
General disorders and administration site conditions	Asthenic conditions	Drug tolerance Oedema Oedema peripheral Malaise Thirst Pyrexia Drug withdrawal syndrome Chills Lymphadenopathy Chest pain ST depression (investigations)

OxyContin 10, 20, 40, 80: The following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

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, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. 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.

Postmarketing Experience:
The following adverse reactions have been identified during post-approval use of controlled-release oxycodone: abuse, addiction, amenorrhea, cholestasis, death, dental caries, increased hepatic enzymes, hyperalgesia, hyponatremia, ileus, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.
Anaphylaxis has been reported with ingredients contained in OxyContin. Advise patients how to recognize such a reaction and when to seek medical attention.

4.9 Overdose

Signs of oxycodone toxicity and overdose are miosis, respiratory depression, hypotension and hallucinations. Circulatory failure and somnolence progressing to stupor or deepening coma, hypotonia, bradycardia, and death may occur in more severe cases.

The effects of overdosage will be potentiated by the simultaneous ingestion of alcohol or other psychotropic drugs.

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 intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children), if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical

response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients.

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

The patient should be observed for at least 6 hours after the last dose of naloxone.

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.

Additional/other considerations:

- 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.

- ***OxyContin*** tablets will continue to release and add to the oxycodone load for up to 12 hours after administration and management of oxycodone overdosage should be modified accordingly. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids
ATC code: NO2A AO5

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, antitussive and sedative.

Endocrine system
Opioids 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 be manifest from these hormonal changes.

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 semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical studies

The efficacy of ***OxyContin*** tablets has been demonstrated in cancer pain, post-operative pain and severe non-malignant pain such as diabetic neuropathy, postherpetic neuralgia, low back pain and osteoarthritis. In the latter indication, treatment was continued for up to 18 months and proved effective in many patients for whom NSAIDs alone provided inadequate relief. The efficacy of ***OxyContin*** tablets in neuropathic pain was confirmed by three placebo-controlled studies.

In patients with chronic non-malignant pain, maintenance of analgesia with stable dosing was demonstrated for up to three years.

5.2 Pharmacokinetic properties

Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. Oxycodone is metabolized in the liver via CYP3A4 and CYP2D6 to noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone is a weak mu opioid agonist. Noroxymorphone is a potent mu opioid agonist; however, it does not cross the blood-brain barrier to a significant extent. Oxymorphone is a potent mu opioid agonist but is present at very low concentrations following oxycodone administration. None of these metabolites are thought to contribute significantly to the analgesic effect of oxycodone.

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

Teratogenicity
Oxycodone had no effect on fertility or early embryonic development in male and female rats at doses as high as 8 mg/kg/d. Also, oxycodone did not induce any deformities in rats at doses as high as 8 mg/kg/d or in rabbits at doses as high as 125 mg/kg/d. Dose-related increases in developmental variations (increased incidences of extra (27) presacral vertebrae and extra pairs of ribs) were observed in rabbits when the data for individual fetuses were analyzed. However, when the same data were analyzed using litters as opposed to individual fetuses, there was no dose-related increase in developmental variations although the incidence of extra presacral vertebrae remained significantly higher in the 125 mg/kg/d group compared to the control group. Since this dose level was associated with severe pharmacotoxic effects in the pregnant animals, the fetal findings may have been a secondary consequence of severe maternal toxicity.

In a study of peri- and postnatal development in rats, maternal body weight and food intake parameters were reduced for doses ≥ 2 mg/kg/d compared to the control group. Body weights were lower in the F1 generation from maternal rats in the 6 mg/kg/d dosing group. There were no effects on physical, reflexological, or sensory developmental parameters or on behavioural and reproductive indices in the F1 pups (the NOEL for F1 pups was 2 mg/kg/d based on body weight effects seen at 6 mg/kg/d). There were no effects on the F2 generation at any dose in the study.

Carcinogenicity
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.

Mutagenicity
The results of *in-vitro* and *in-vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically.

Oxycodone was not genotoxic in a bacterial mutagenicity assay or in an *in-vivo* micronucleus assay in the mouse. Oxycodone produced a positive response in the *in-vitro* mouse lymphoma assay in the presence of rat liver S9 metabolic activation at dose levels greater than 25 µg/mL. Two *in-vitro* chromosomal aberrations assays with human lymphocytes were conducted. In the first assay, oxycodone was negative without metabolic activation but was positive with S9 metabolic activation at the 24 hour time point but not at other time points or at 48 hour after exposure. In the second assay, oxycodone did not show any clastogenicity either with or without metabolic activation at any concentration or time point.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Hypromellose
Titanium dioxide
Macrogol

In addition the tablets contain the following:

OxyContin 5 contains: Brilliant blue (E133), lactose, povidone, talc, ammonio methacrylate co-polymer, glyceryl triacetate, stearyl alcohol.
OxyContin 10 contains: Hydroxypropylcellulose, polyethylene oxide.
OxyContin 20 contains: Polysorbate 80, red iron oxide (E172), polyethylene oxide.
OxyContin 40 contains: Polysorbate 80, yellow iron oxide (E172), polyethylene oxide.
OxyContin 80 contains: Hydroxypropylcellulose, yellow iron oxide (E172), indigo carmine (E132), polyethylene oxide.

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Do not store above 25°C.

6.4 Nature and contents of container

PVC blister packs with aluminium foil backing containing 20 tablets.

6.5 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder and numbers

OxyContin 5 1317530830 (This strength is manufactured by Napp Pharmaceuticals, England).
OxyContin 10 1007128431
OxyContin 20 1007028432
OxyContin 40 1090129255
OxyContin 80 1089829256

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The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in February 2013.