LONGTEC 5MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0145

LONGTEC 10MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0146

LONGTEC 20MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0147

LONGTEC 40MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0148

LONGTEC 80MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0149

UKPAR

TABLE OF CONTENTS

LONGTEC 5MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0145

LONGTEC 10MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0146

LONGTEC 20MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0147

LONGTEC 40MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0148

LONGTEC 80MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0149

LAY SUMMARY

The MHRA granted NAPP Pharmaceuticals Limited Marketing Authorisation (licences) for the medicinal products Longtec 5mg, 10mg, 20mg, 40mg, and 80mg Film-Coated Prolonged Release Tablets (PL 16950/0145-9). These are prescription only medicines (POM).

Longtec tablets are used for relieve of moderate to severe pain over a period of 12 hours.

They contain the active ingredient oxycodone which belongs to a group of medicines called strong analgesics or painkillers.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Longtec Film-Coated Prolonged Release Tablets outweigh the risks, hence marketing authorisations have been granted.

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PL 16950/0146

LONGTEC 20MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0147

LONGTEC 40MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0148

LONGTEC 80MG FILM-COATED PROLONGED RELEASE TABLETS
PL 16950/0149

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Longtec 5mg, 10mg, 20mg, 40mg, and 80mg Film-Coated Prolonged Release Tablets (PL 16950/0145-9) to NAPP Pharmaceuticals Limited on 15th February 2008. These are prescription only medicines (POM) used for the treatment of moderate to severe pain in patients with cancer and post-operative pain. It is also indicated for the treatment of severe pain requiring the use of a strong opioid.

These applications were submitted under Article 10(c) of Directive 2001/83/EC, claiming to possess the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form of an already authorised product. The relevant product in the UK is Oxycontin Tablets 5mg, 10mg, 20mg, 40mg, and 80mg (PL 16950/0097-0100 & 0123) currently authorised to Napp Pharmaceuticals Ltd in March 1999 (10, 20, 40 & 80 mg) and May 2002 (5 mg).

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.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 16950/0145-9
PROPRIETARY NAME: Longtec 5, 10, 20, 40 and 80mg Film-Coated Prolonged Release Tablets
COMPANY NAME: Napp Pharmaceuticals Limited
E.C. ARTICLE: Article 10 (c) of Directive 2001/83/EC
LEGAL STATUS: POM

1 INTRODUCTION

These national simple BROMI abridged applications are for tablets containing 5, 10, 20, 40, and 80 mg of opiod analgesic oxycodone hydrochloride. The product is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain. It is also indicated for the treatment of severe pain requiring the use of a strong opioid.

These applications were submitted under Article 10(c) of Directive 2001/83/EC, claiming to possess the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form of an already authorised product. The relevant product in the UK is Oxycontin Prolonged Release Tablets 5, 10, 20, 40 and 80 mg (PL 16950/0097-0100 & 0123) currently authorised to Napp Pharmaceuticals Ltd in March 1999 (10, 20, 40 & 80 mg) and May 2002 (5 mg).

2 MARKETING AUTHORISATION APPLICATION (MAA)

2.1 Name(s)

The proposed names of the products are Longtec 5, 10, 20, 40 and 80mg Film-Coated, Prolonged Release Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains the active ingredient oxycodone hydrochloride. It will be packaged into PVC/aluminium blisters only. The packagings are identical to the blister packaging used for the reference product.

The respective SPC have indicated that Longtec Film-Coated Prolonged Release Tablets are packed in pack sizes of 28 and 56 tablets. The same pack sizes are stated in the reference product. The proposed shelf life is 3 years which is identical to the reference product. The proposed storage condition is also consistent with the details registered for the cross-reference product.

2.3 Legal status

The products are Prescription only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is NAPP Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 0GW, UK

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.
A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification conformed to current Ph Eur monograph for oxycodone hydrochloride and was consistent with that of the reference product.

Current Ph Eur certificate of suitability for the drug substance manufacturer has been provided to support the sources of active substance. This manufacturer is in line with the reference product.

2.10 TSE Compliance
The active ingredient supplier has confirmed that no materials of human or animal origin have been used in the manufacture of oxycodone hydrochloride.

Appropriate TSE declarations have been provided for magnesium stearate and lactose monohydrate used in the finished product.

2.11 Bioequivalence / Bioavailability
No bioavailability and bioequivalence data are required to support this informed consent application as the proposed product is manufactured to the same formula utilising the same process. The finished product manufacturing site is also identical to that used by the reference product.

3 EXPERT REPORT

The applicant has included detailed expert reports of the application. Signed declarations and copies of the experts' CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs are consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/BLISTER

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

The result of user testing has been provided.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the applications is acceptable. Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none is required for an application of this type.

CLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none is required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for application of this type.

EFFICACY

These applications are identical to previously granted applications for Oxycontin Prolonged Release Tablets.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with Oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

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PL 16950/0148

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PL 16950/0149

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 5th February 2007
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 11th March 2007
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 12th April 2007.
4	The applicant responded to the MHRA's request, providing further information for the quality section on 11th May 2007.
5	The application was determined on 15th February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Longtec 5 mg film-coated, prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4.5 mg of oxycodone as 5 mg of oxycodone hydrochloride.
For a full list of excipients, see Section 6.1.
This product contains lactose monohydrate (see section 4.3 Contra-indications).

3. PHARMACEUTICAL FORM

Film-coated, prolonged release tablet.
Light blue, round, convex tablets marked OC on one side and 5 on the other.

4. 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

Longtec tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
Longtec 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.

Longtec tablets are not intended for use as a prn analgesic.
Increasing severity of pain will require an increased dosage of ***Longtec*** 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 in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of ***Longtec*** 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 daily have been recorded.

Patients receiving oral morphine before ***Longtec*** tablets 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 ***Longtec*** 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 ***Longtec*** tablets 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 ***Longtec*** tablets 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. Contraindications

Hypersensitivity to any of the constituents, 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 <10ml/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. ***Longtec*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Longtec*** 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 ***Longtec*** tablets for 24 hours before surgery. If further treatment with ***Longtec*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

Longtec tablets 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, ***Longtec*** 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. ***Longtec*** 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.

Oxycodone 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.

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

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** 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 medicinal products and other forms of interaction

Oxycodone, 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

Longtec 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. ***Longtec*** 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	Vertigo

	Confusion Asthenia Faintness Dizziness Sedation Anxiety Abnormal dreams Nervousness Insomnia Thought abnormalities Drowsiness Twitching	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 ***Longtec*** 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.

Longtec 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 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 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 that 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.

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.

Longtec 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. Gastric contents may therefore 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: N02A A05
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 ***Longtec*** 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 oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day.

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

Longtec 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 ***Longtec*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

Longtec 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 ***Longtec*** 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Povidone K30
Ammoniomethacrylate co-polymer
Sorbic acid
Glycerol triacetate
Stearyl alcohol
Talc
Magnesium stearate

Film coat (Opadry Blue 06B20843)
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Brilliant blue (E133)

6.2. Incompatibilities

Not applicable.

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 or 56 tablets).
Not all pack sizes may be marketed.

6.6 Instruction for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 16950/0145

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2008

10 DATE OF REVISION OF THE TEXT

15/02/2008

1. NAME OF THE MEDICINAL PRODUCT

Longtec 10 mg film-coated, prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 9 mg of oxycodone as 10 mg of oxycodone hydrochloride.
For a full list of excipients, see Section 6.1.
This product contains lactose monohydrate (see section 4.3 Contra-indications).

3. PHARMACEUTICAL FORM

Film-coated, prolonged release tablet.
White, round, convex tablets marked OC on one side and 10 on the other.

4. 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

Longtec tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
Longtec 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.

Longtec tablets are not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of ***Longtec*** tablets, using the 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 ***Longtec*** 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 daily have been recorded.

Patients receiving oral morphine before ***Longtec*** tablets 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 ***Longtec*** 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 ***Longtec*** tablets 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. Opioid naïve patients should be started on ***Longtec*** tablets 5 mg or ***OxyNorm*** liquid 2.5 mg 6-hourly and titrated to pain relief as described before.

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, 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 <10ml/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. ***Longtec*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Longtec*** 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 ***Longtec*** tablets for 24 hours before surgery. If further treatment with ***Longtec*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

Longtec tablets 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, ***Longtec*** 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. ***Longtec*** 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.

Oxycodone 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.

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

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** 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 medicinal products and other forms of interaction

Oxycodone, 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

Longtec 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. ***Longtec*** 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	Vertigo
	Confusion	Hallucinations
	Asthenia	Hypertonia
	Faintness	Disorientation
	Dizziness	Mood changes
	Sedation	Restlessness
	Anxiety	Agitation
	Abnormal dreams	Depression
	Nervousness	Tremor
	Insomnia	Withdrawal syndrome
	Thought abnormalities	Amnesia
	Drowsiness	Hypoaesthesia
	Twitching	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	Overdose may produce respiratory depression
	Dyspnoea	
	Decreased cough reflex	
Dermatological	Rash	Dry skin
	Pruritus	Exfoliative dermatitis
		Urticaria
General	Sweating	Facial flushing
	Chills	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 ***Longtec*** 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.

Longtec 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 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 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 that 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.

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.

Longtec 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. Gastric contents may therefore 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: N02A A05

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 ***Longtec*** 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 oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day.

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

Longtec 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 ***Longtec*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

Longtec tablets 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 ***Longtec*** 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Povidone K30
Ammoniomethacrylate co-polymer
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film coat (Opadry white Y-5-18024A

Hypromellose (E464)
Hydroxypropylcellulose
Titanium Dioxide (E171)
Macrogol 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Three years

6.4. Special precautions for storage

Do not store above 25°C

6.6. Nature and contents of container

Polypropylene containers with polyethylene lids (containing 28, 56 or 112 tablets).
PVC blister packs with aluminium foil backing (containing 28, 56 or 112 tablets).

Not all pack sizes may be marketed.

6.6 Instruction for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 16950/0146

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2008

10 DATE OF REVISION OF THE TEXT

15/02/2008

1 NAME OF THE MEDICINAL PRODUCT

Longtec 20 mg film-coated, prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 18.0 mg of oxycodone as 20 mg of oxycodone hydrochloride.
For a full list of excipients see Section 6.1.
This product contains lactose monohydrate (see section 4.3 Contra-indications).

3 PHARMACEUTICAL FORM

Film coated, prolonged release tablet.
Pink, round, convex tablets marked OC on one side and 20 on the other.

4 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

Longtec tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
Longtec 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.

Longtec tablets are not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of ***Longtec*** tablets, using the 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 ***Longtec*** 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 daily have been recorded.

Patients receiving oral morphine before ***Longtec*** tablets 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 ***Longtec*** 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 Napp ***Longtec*** tablets 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. Opioid naïve patients should be started on ***Longtec*** tablets 5 mg 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 Contraindications

Hypersensitivity to any of the constituents 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 <10ml/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, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, pancreatitis, chronic renal and hepatic disease, or severe pulmonary disease, and debilitated elderly and infirm patients. ***Longtec*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Longtec*** 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 ***Longtec*** tablets for 24 hours before surgery. If further treatment with ***Longtec*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

Longtec tablets 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, ***Longtec*** 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. ***Longtec*** 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.

Oxycodone 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.

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

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** 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 Interaction with other medicinal products and other forms of interaction

Oxycodone, 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

Longtec 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. *Longtec* 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 Longtec 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.

Longtec 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 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 that 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.

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.

Longtec 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. Gastric contents may therefore 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: N02A A05

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 ***Longtec*** 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 oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day.

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

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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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Ammoniomethacrylate co-polymer
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film coat (Opadry pink YS-1-14518-A)

Hypromellose (E464)
Titanium dioxide (E171)
Polysorbate 80
Macrogol 400
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

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

Polypropylene containers with polyethylene lids (containing 28, 56 or 112 tablets).
PVC blister packs with aluminium foil backing (containing 28, 56 or 112 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 16950/0147

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2008

10 DATE OF REVISION OF THE TEXT

15/02/2008

1 NAME OF THE MEDICINAL PRODUCT

Longtec 40 mg film-coated, prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 36.0 mg of oxycodone as 40 mg of oxycodone hydrochloride.
For a full list of excipients see Section 6.1.
This product contains lactose monohydrate (see section 4.3 Contra-indications).

3 PHARMACEUTICAL FORM

Film coated, prolonged release tablet.
Yellow, round, convex tablets marked OC on one side and 40 on the other.

4 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

Longtec tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
Longtec 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.

Longtec tablets are not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of ***Longtec*** tablets, using the 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 ***Longtec*** 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 daily have been recorded.

Patients receiving oral morphine before ***Longtec*** tablets 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 ***Longtec*** 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 ***Longtec*** tablets 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. Opioid naïve patients should be started on ***Longtec*** tablets 5 mg 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 Contraindications

Hypersensitivity to any of the constituents 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 <10ml/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, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, pancreatitis, chronic renal and hepatic disease, or severe pulmonary disease, and debilitated elderly and infirm patients. ***Longtec*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Longtec*** 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 ***Longtec*** tablets for 24 hours before surgery. If further treatment with ***Longtec*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

Longtec tablets 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, ***Longtec*** 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. ***Longtec*** 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.

Oxycodone 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.

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

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** 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 Interaction with other medicinal products and other forms of interaction

Oxycodone, 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

Longtec 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. ***Longtec*** 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 Longtec 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.

Longtec 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 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 intial 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 that 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.

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.

Longtec 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. Gastric contents may therefore 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: N02A A05

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 ***Longtec*** 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 oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day.

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

Longtec 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 ***Longtec*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

Longtec tablets 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 ***Longtec*** 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Ammoniomethacrylate co-polymer
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film coat (Opadry yellow YS-1-12525-A)

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

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

Polypropylene containers with polyethylene lids (containing 28, 56 or 112 tablets).
PVC blister packs with aluminium foil backing (containing 28, 56 or 112 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 16950/0148

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2008

10 DATE OF REVISION OF THE TEXT

15/02/2008

1 NAME OF THE MEDICINAL PRODUCT

Longtec 80 mg film-coated, prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 72.0 mg of oxycodone as 80 mg of oxycodone hydrochloride.
For a full list of excipients see Section 6.1.
This product contains lactose monohydrate (see section 4.3 Contra-indications).

3 PHARMACEUTICAL FORM

Film coated, prolonged release tablet.
Green, round, convex tablets marked OC on one side and 80 on the other.

4 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

Longtec tablets must be swallowed whole, and not chewed.

Elderly and adults over 18 years:
Longtec 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.

Longtec tablets are not intended for use as a prn analgesic.

Increasing severity of pain will require an increased dosage of ***Longtec*** tablets, using the 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 ***Longtec*** 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 daily have been recorded.

Patients receiving oral morphine before ***Longtec*** tablets 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 ***Longtec*** 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 ***Longtec*** tablets 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. Opioid naïve patients should be started on ***Longtec*** tablets 5 mg 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 Contraindications

Hypersensitivity to any of the constituents 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 <10ml/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. ***Longtec*** tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, ***Longtec*** 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 ***Longtec*** tablets for 24 hours before surgery. If further treatment with ***Longtec*** tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

Longtec tablets 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.

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. ***Longtec*** 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.

Oxycodone 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.

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

Longtec tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed, or crushed ***Longtec*** 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 Interaction with other medicinal products and other forms of interaction

Oxycodone, like other opioids, potentiates the effects of tranquillisers, anaesthetics, hypnotics, anti-depressants, sedatives, phenothiazines, neouroleptic 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

Longtec 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. ***Longtec*** 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	Vertigo Hallucinations Hypertonia Disorientation

	Dizziness Sedation Anxiety Abnormal dreams Nervousness Insomnia Thought abnormalities Drowsiness Twitching	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 Longtec 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.

Longtec 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 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 at the dose 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the intial 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 that 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.

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.

Longtec 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. Gastric contents may therefore 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: N02A A05

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 ***Longtec*** 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 oxycodone is 4.5 hours, which leads to steady-state being achieved in about one day.

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

Longtec 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 ***Longtec*** tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

Longtec tablets 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 ***Longtec*** 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Ammoniomethacrylate co-polymer
Sorbic acid
Triacetin
Stearyl alcohol
Talc
Magnesium stearate

Film Coat (Opadry green Y-5-11167-A)

Hypromellose (E464)
Hydroxypropylcellulose
Titanium dioxide (E171)
Macrogol 400
Iron oxide (E172)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

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

Polypropylene containers with polyethylene lids (containing 28, 56 or 112 tablets).
PVC blister packs with aluminium foil backing (containing 28, 56 or 112 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 16950/0149

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2008

10 DATE OF REVISION OF THE TEXT

15/02/2008

PATIENT INFORMATION LEAFLET

Package leaflet: Information for the user

***Longtec*® 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, film-coated, prolonged release tablets**
Oxycodone hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Longtec* tablets are and what they are used for

These tablets have been prescribed for you by your doctor to relieve moderate to severe pain over a period of 12 hours. They contain the active ingredient oxycodone which belongs to a group of medicines called strong analgesics or 'painkillers'. The other ingredients are listed in section 6 of this leaflet.

***Longtec* tablets are designed to work properly over 12 hours when swallowed whole. If a tablet is broken, crushed, dissolved or chewed, the entire 12-hour dose will be absorbed rapidly into your body. This can be dangerous, causing serious problems such as an overdose, which may be fatal.**

2. Before you take *Longtec* tablets

Do not take *Longtec* tablets:
- if you are allergic (hypersensitive) to oxycodone, or any of the other ingredients of *Longtec* tablets;
- if you have breathing problems, such as respiratory depression, chronic obstructive airways disease, chronic bronchial asthma or severe pulmonary disease, unless otherwise recommended by your doctor;
- if you have a head injury that causes a severe headache or makes you feel sick. This is because the tablets may make these symptoms worse or hide the extent of the head injury;
- if you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen;
- if you have a heart problem after long-term lung disease (cor pulmonale);
- if you have severe kidney problems or moderate to severe liver problems. If you have other long term kidney or liver problems you should only take *Longtec* tablets if recommended by your doctor;
- if you have ongoing problems with constipation;
- if you are taking a specific type of antidepressant known as a monoamine oxidase inhibitor, or you have taken this type of medicine in the last two weeks.

Children and adolescents under 18 years old should not take the tablets.

If you are going to have an operation, please tell the doctor at the hospital that you are taking these tablets.

Take special care with *Longtec* tablets

Before treatment with *Longtec* tablets tell your doctor or pharmacist:
- if you have an under-active thyroid gland (hypothyroidism), as you may need a lower dose of *Longtec* tablets;
- if you have a severe headache or feel sick as this may indicate that the pressure in your skull is increased;
- if you have low blood pressure (hypotension);
- if you have a mental disorder as a result of an infection (toxic psychosis);
- if you have inflammation of the pancreas (pancreatitis) or problems with your gall bladder;
- if you have inflammatory bowel disease;
- if you have prostate problems;
- if you have poor adrenal gland function;
- if you have an addiction to alcohol or drugs;
- if you have previously suffered from withdrawal symptoms such as agitation, anxiety, shaking and sweating, upon stopping taking alcohol or drugs.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you take *Longtec* tablets with some other medicines, the effect of *Longtec* tablets or the other medicine may be changed.

Tell your doctor or pharmacist:
- if you are taking medicines to help you sleep (for example tranquillisers, hypnotics or sedatives);
- if you have recently been given an anaesthetic;
- if you are taking medicines to treat depression;
- if you are taking medicines to treat psychiatric or mental disorders;
- if you are taking other strong analgesics or 'painkillers';
- if you have recently been given a muscle relaxant;
- if you are taking medicines to treat high blood pressure;
- if you are taking quinidine (a medicine to treat a fast heart beat);
- if you are taking cimetedine (a medicine for ulcers, indigestion or heartburn);
- if you are taking antifungal medicines (such as ketoconazole);
- if you are taking antibiotics (such as erythromycin).

Taking *Longtec* tablets with alcohol

Drinking alcohol during your treatment with *Longtec* tablets may make you sleepy. If you are affected you should avoid drinking alcohol.

Pregnancy and breast feeding

Do not take *Longtec* tablets if you are pregnant or breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel sleepy when you first start taking *Longtec* tablets, or when changing to a higher dose. If you are affected you should not drive or use machinery.

Important information about some of the ingredients of *Longtec* tablets

These tablets contain lactose which is a form of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking these tablets.

3. How to take *Longtec* tablets

Always take *Longtec* tablets exactly as your doctor has told you. The label on your medicine will tell you how many tablets to take and how often.

The usual starting dose for adults over 18 years old is one 10 mg tablet every 12 hours. However, your doctor will prescribe the dose required to treat your pain. If you find that you are still in pain whilst taking *Longtec* tablets discuss this with your doctor.

Do not exceed the dose recommended by your doctor. You should check with your doctor or pharmacist if you are not sure.

Swallow your tablets whole with water. **Do not chew, crush or dissolve them.**

You should take your tablets every 12 hours. For instance, if you take a tablet at 8 o'clock in the morning, you should take your next tablet at 8 o'clock in the evening.

You must only take *Longtec* tablets by mouth. The tablets should never be crushed or injected as this may lead to serious side effects, which may be fatal.

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If you take more *Longtec* tablets than you should or if someone accidentally swallows your tablets

Call your doctor or hospital straight away. People who have taken an overdose may feel very sleepy and sick. They may also have breathing difficulties leading to unconsciousness or even death and may need emergency treatment in hospital. When seeking medical attention make sure that you take this leaflet and any remaining tablets with you to show to the doctor.

If you forget to take your *Longtec* tablets

If you remember within 4 hours of the time your tablet was due, take your tablet straight away. Take your next tablet at your normal time. If you are more than 4 hours late, please call your doctor or pharmacist for advice. Do not take a double dose to make up for a forgotten tablet.

If you stop taking *Longtec* tablets

You should not suddenly stop taking these tablets unless your doctor tells you to. If you want to stop taking your tablets, discuss this with your doctor first. They will tell you how to do this, usually by reducing the dose gradually so you do not experience unpleasant effects.

If you have any further questions on the use of *Longtec* tablets, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, *Longtec* tablets can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions, although serious allergic reactions are rare. Tell your doctor immediately if you get any sudden wheeziness, difficulties in breathing, swelling of the eyelids, face or lips, rash or itching especially those covering your whole body.

As with all strong painkillers, there is a risk that you may become addicted or reliant on *Longtec* tablets.

Common side effects

(Probably affecting more than 1 in 100 people taking *Longtec* tablets)

Most people will have constipation when they take *Longtec* tablets. Your doctor can prescribe a laxative to overcome this problem.

You may feel sick or vomit (be sick) when you take these tablets, this should normally wear off after a few days however your doctor can prescribe an anti-vomiting medicine if it continues to be a problem.

You may find that you feel more sleepy than normal when you start taking your tablets or when your dose is increased. This should wear off after a few days.

The following side effects have also been commonly reported in patients treated with *Longtec* tablets:
- Dry mouth, loss of appetite, indigestion, abdominal pain or discomfort, diarrhoea.
- Headache, confusion, a feeling of unusual weakness, dizziness, a feeling of faintness, especially on standing up, anxiety, nervousness, twitching, difficulty in sleeping, abnormal thoughts or dreams.
- Difficulty breathing or wheezing, shortness of breath, decreased cough reflex.
- Rash, itchy skin.
- Sweating, chills.

Uncommon side effects

(Probably affecting fewer than 1 in 100 people taking *Longtec* tablets)
- Difficulty in swallowing, belching, hiccups, wind, gastrointestinal disorders (e.g. upset stomach), changes in taste.
- A feeling of dizziness or 'spinning', hallucinations, mood changes, depression, a feeling of extreme happiness, restlessness, agitation, generally feeling unwell, loss of memory, shaking, difficulties with speech, reduced sensitivity to pain or touch, tingling in the hands and feet, seizures, fits or convulsions, blurred vision.
- Difficulty passing urine, impotence, decreased sexual drive, absence of menstrual periods.
- Fast, irregular heart beat, low blood pressure, flushing of the skin.
- Dehydration, thirst, swelling of the hands, ankles or feet.
- Dry skin, severe flaking or peeling of the skin.
- Redness of the face, reduction in size of the pupils in the eye, muscle spasm, high temperature.
- Withdrawal symptoms such as agitation, anxiety, shaking and sweating upon stopping taking *Longtec* tablets.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store *Longtec* tablets

Keep out of the reach and sight of children. Accidental overdose by a child is dangerous and may be fatal.

Do not use any tablets after the expiry date which is stated on the carton. EXP 08.2010 means that you should not take the tablets after the last day of that month i.e. August 2010.

Do not store your tablets above 25°C.

Do not take your tablets if they are broken or crushed as this can be dangerous and can cause serious problems such as overdose.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What *Longtec* tablets contain

The active ingredient is oxycodone hydrochloride. Each tablet contains 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of oxycodone hydrochloride.

The other ingredients are:
- Lactose monohydrate
- Povidone K30
- Ammoniomethacrylate polymer
- Sorbic acid
- Triacetin
- Stearyl alcohol
- Talc
- Magnesium stearate
- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol 400

In addition, the tablet coatings contain the following:

5 mg – brilliant blue (E133)

10 mg – hydroxypropylcellulose

20 mg & 40 mg – polysorbate 80 (E433), and iron oxide (E172)

80 mg – hydroxypropylcellulose, iron oxide (E172), and indigo carmine (E132)

What *Longtec* tablets look like and the contents of the pack

Longtec tablets are round, bi-convex, film coated tablets.
- 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.

In each box there are 28 or 56 tablets.

Marketing Authorisation Holder and Manufacturer

The tablets are made by Bard Pharmaceuticals Limited for the marketing authorisation holder Napp Pharmaceuticals Limited, both at Cambridge Science Park, Milton Road, Cambridge CB4 0GW, UK.

This leaflet was last revised in 04/2007

Longtec tablets are the subject of European Patents (UK) Numbers 0 253 164, 0 576 643 and European Patent Application 96103992.3.

® The NAPP device (logo) and *Longtec* are Registered Trade Marks.

NAPP

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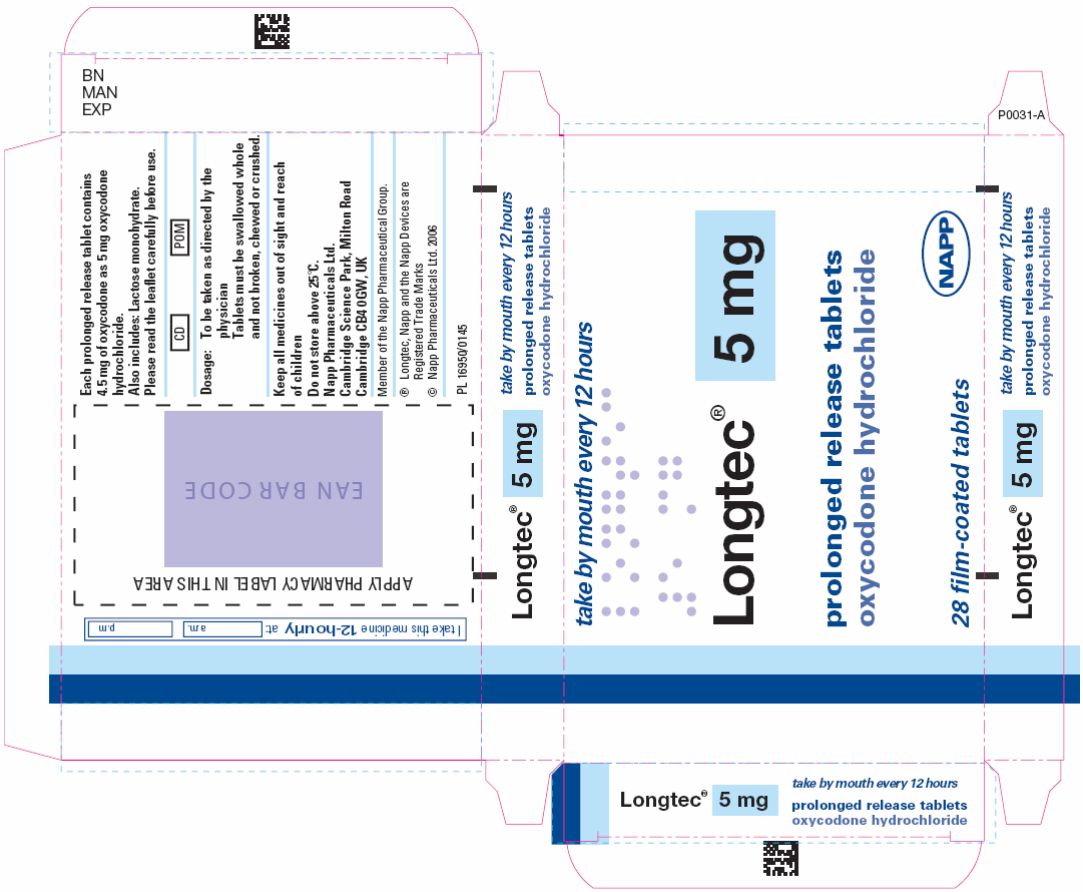
LABELLING


BN
MAN
EXP
Each prolonged release tablet contains 4.5 mg of oxycodone as 5 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep all medicines out of sight and reach of children
Do not store above 25°C.
Napp Pharmaceuticals Ltd.
Cambridge Science Park, Milton Road
Cambridge CB4 0GW, UK
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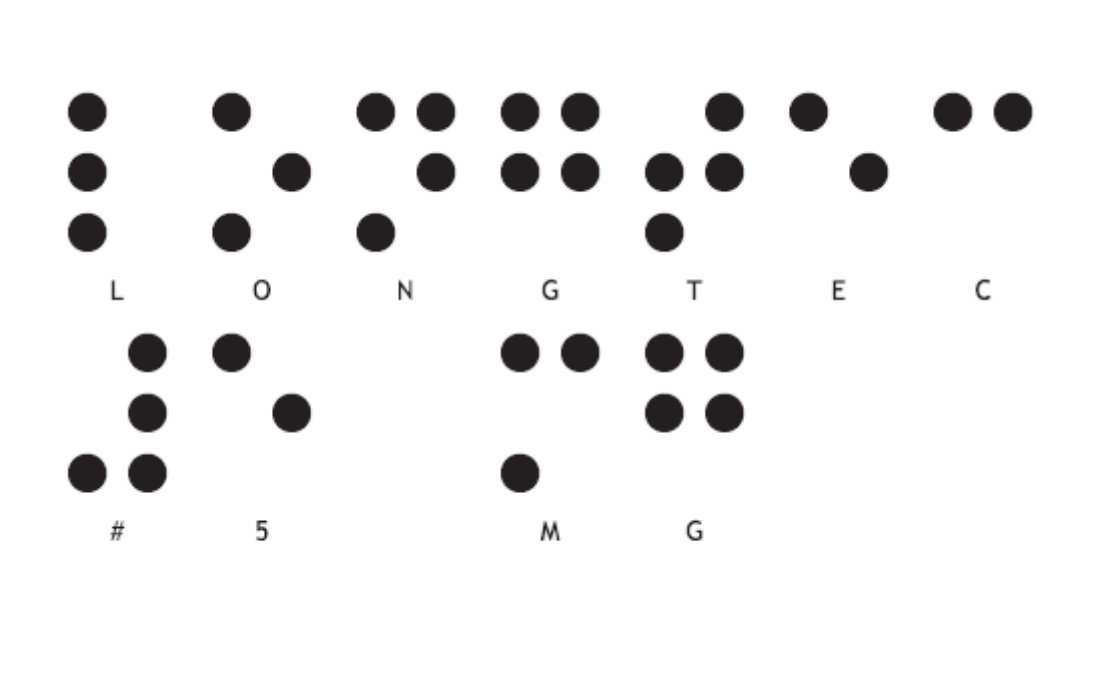
PL 16950/0145
EAN BAR CODE
APPLY PHARMACY LABEL IN THIS AREA
Take this medicine at 12-hourly
a.m.
p.m.
Longtec® 5 mg
take by mouth every 12 hours
prolonged release tablets
oxycodone hydrochloride
P0031-A
take by mouth every 12 hours
Longtec® 5 mg
prolonged release tablets
oxycodone hydrochloride
NAPP
28 film-coated tablets
Longtec® 5 mg
take by mouth every 12 hours
prolonged release tablets
oxycodone hydrochloride
Longtec® 5 mg
take by mouth every 12 hours
prolonged release tablets
oxycodone hydrochloride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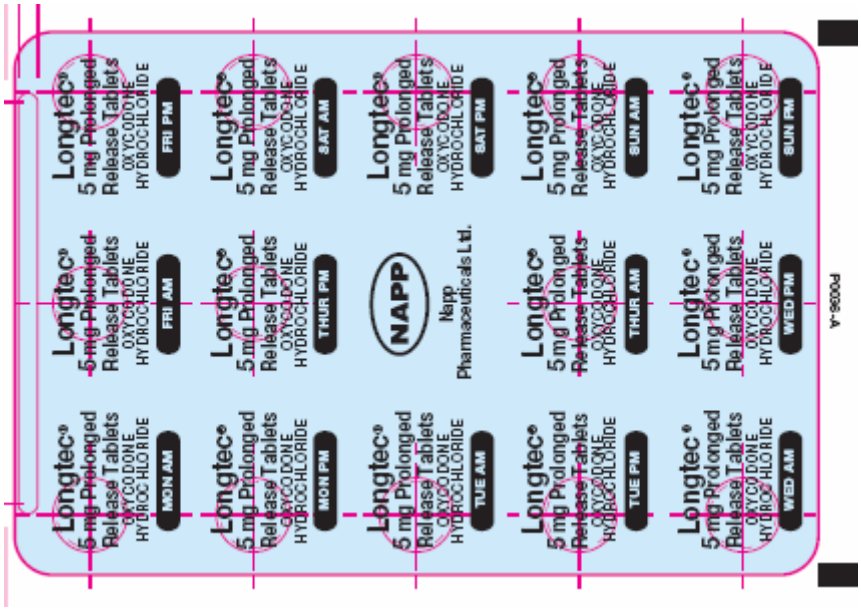
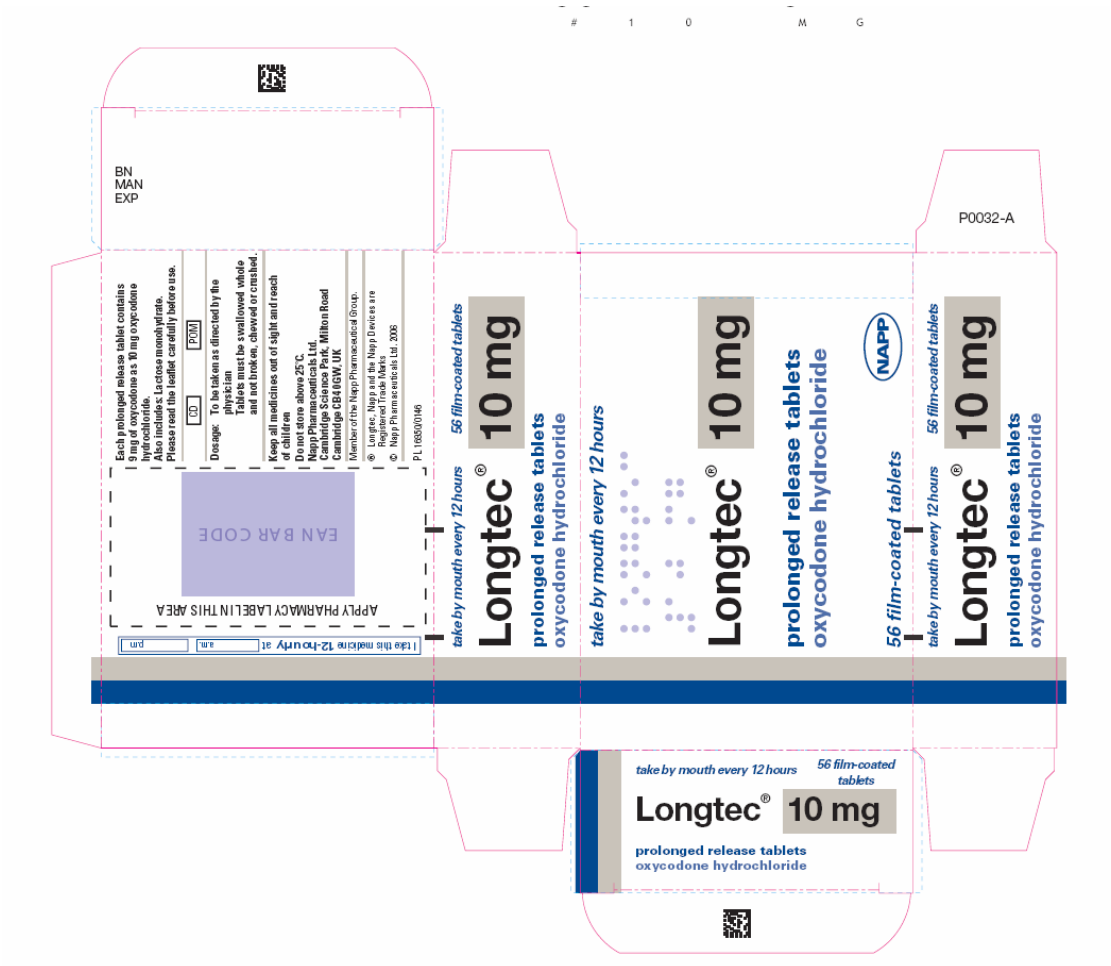
5 M G


Longtec® 5 mg Prolonged Release Tablets OXYCODONE HYDROCHLORIDE
MON AM
TUE AM
WED AM
THUR AM
FRI AM
SAT AM
SUN AM
MON PM
TUE PM
WED PM
THUR PM
FRI PM
SAT PM
SUN PM
NAPP
Napp Pharmaceuticals Ltd.
P0036-A


BN
MAN
EXP
P0032-A
Each prolonged release tablet contains 9 mg of oxycodone as 10 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep all medicines out of sight and reach of children
Do not store above 25°C.
Napp Pharmaceuticals Ltd.
Cambridge Science Park, Milton Road
Cambridge CB4 0GW, UK
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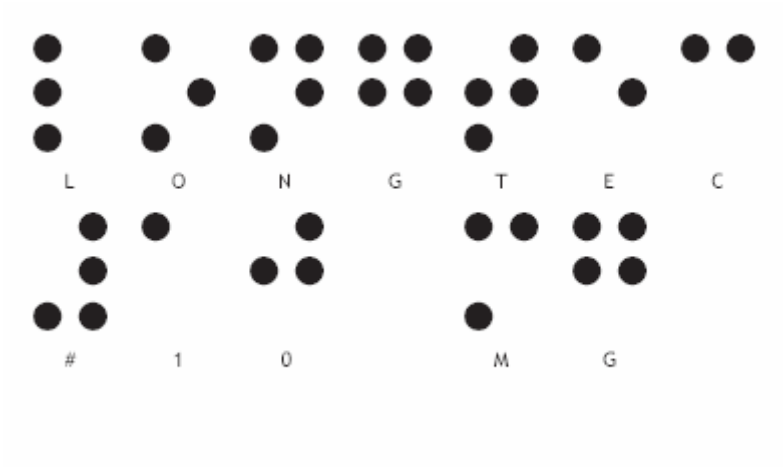
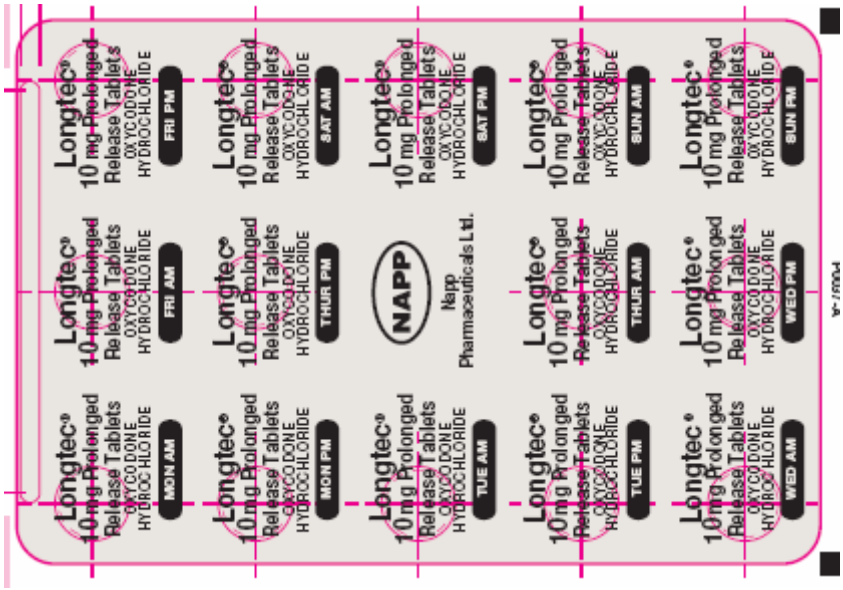
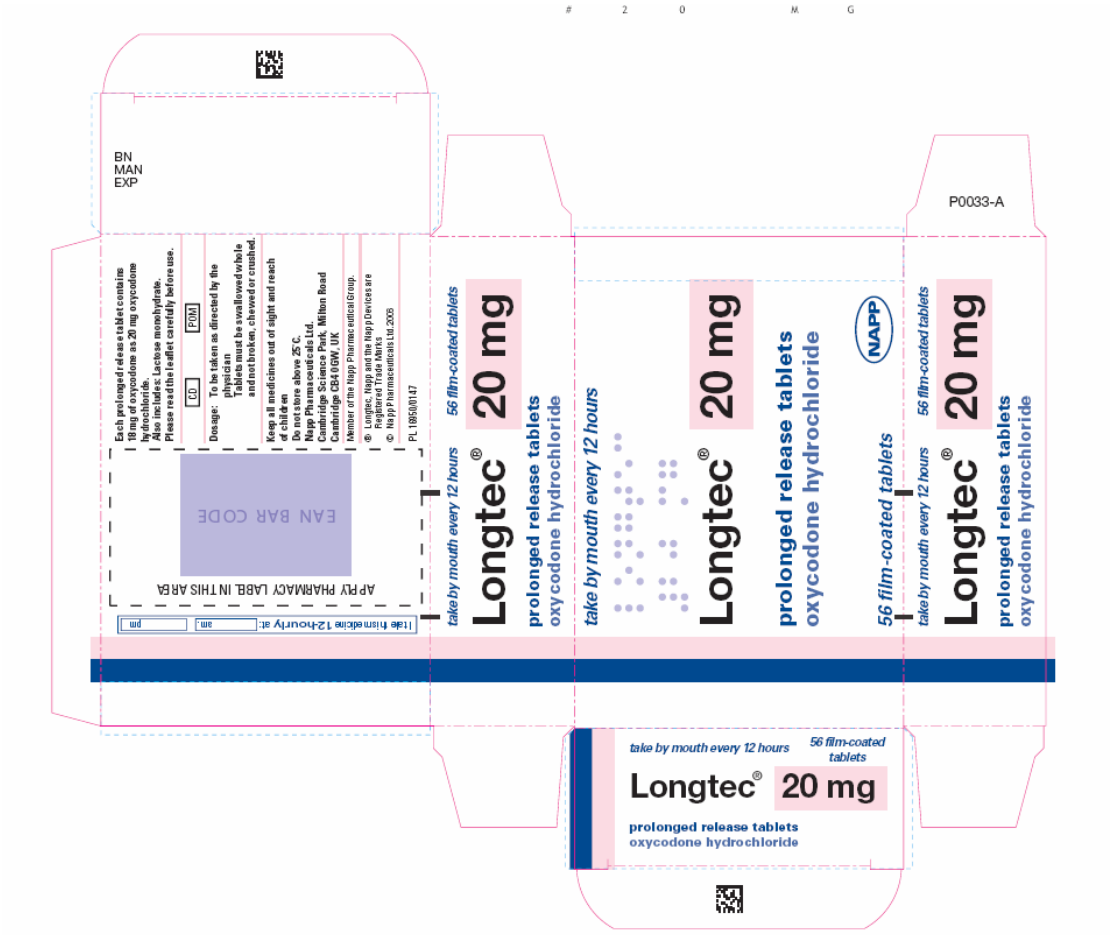
PL 16950/0146
EAN BAR CODE
APPLY PHARMACY LABEL IN THIS AREA
I take this medicine 12-hourly at
am
pm
take by mouth every 12 hours
56 film-coated tablets
Longtec® 10 mg
prolonged release tablets
oxycodone hydrochloride
NAPP


L O N G T E C
1 0 M G


Longtec® 10 mg Prolonged Release Tablets OXYCODONE HYDROCHLORIDE
MON AM
MON PM
TUE AM
TUE PM
WED AM
WED PM
THUR AM
THUR PM
FRI AM
FRI PM
SAT AM
SAT PM
SUN AM
SUN PM
NAPP
Napp Pharmaceuticals Ltd.


BN
MAN
EXP
P0033-A
Each prolonged release tablet contains 18mg of oxycodone as 20 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
POM
CD
Dosage: To be taken as directed by the physician
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep all medicines out of sight and reach of children
Do not store above 25°C.
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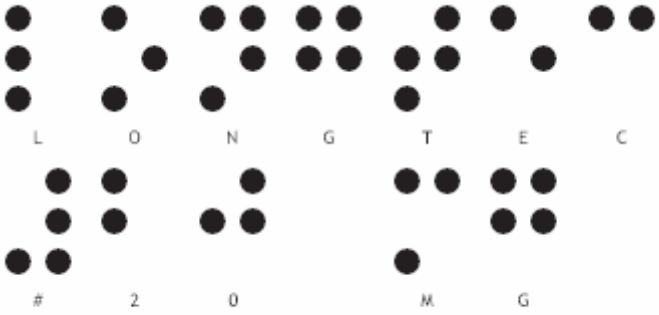
® Longtec, Napp and the Napp Devices are Registered Trade Marks
© Napp Pharmaceuticals Ltd. 2005
PL 16950/0147
EAN BAR CODE
APPLY PHARMACY LABEL IN THIS AREA
take this medicine 12-hourly at:
am
pm
56 film-coated tablets
20 mg
take by mouth every 12 hours
Longtec®
prolonged release tablets
oxycodone hydrochloride
NAPP


L O N G T E C
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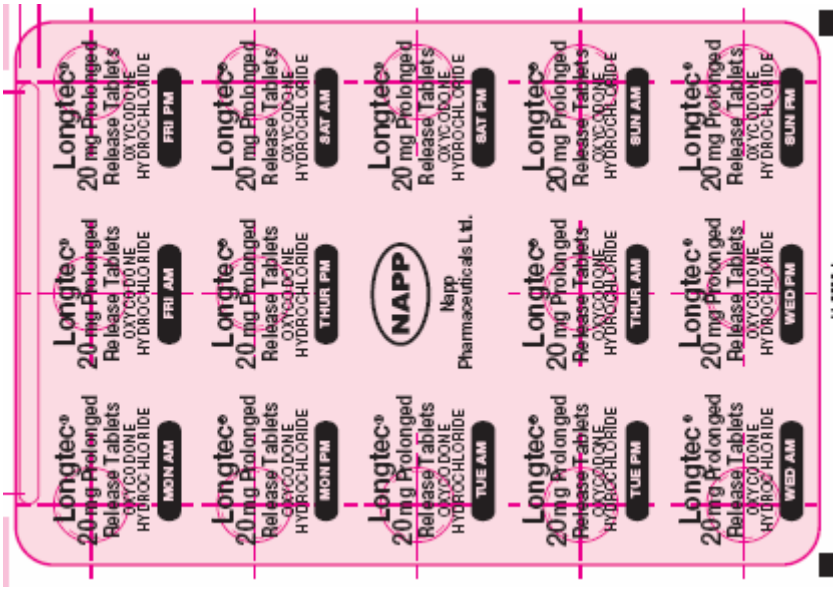
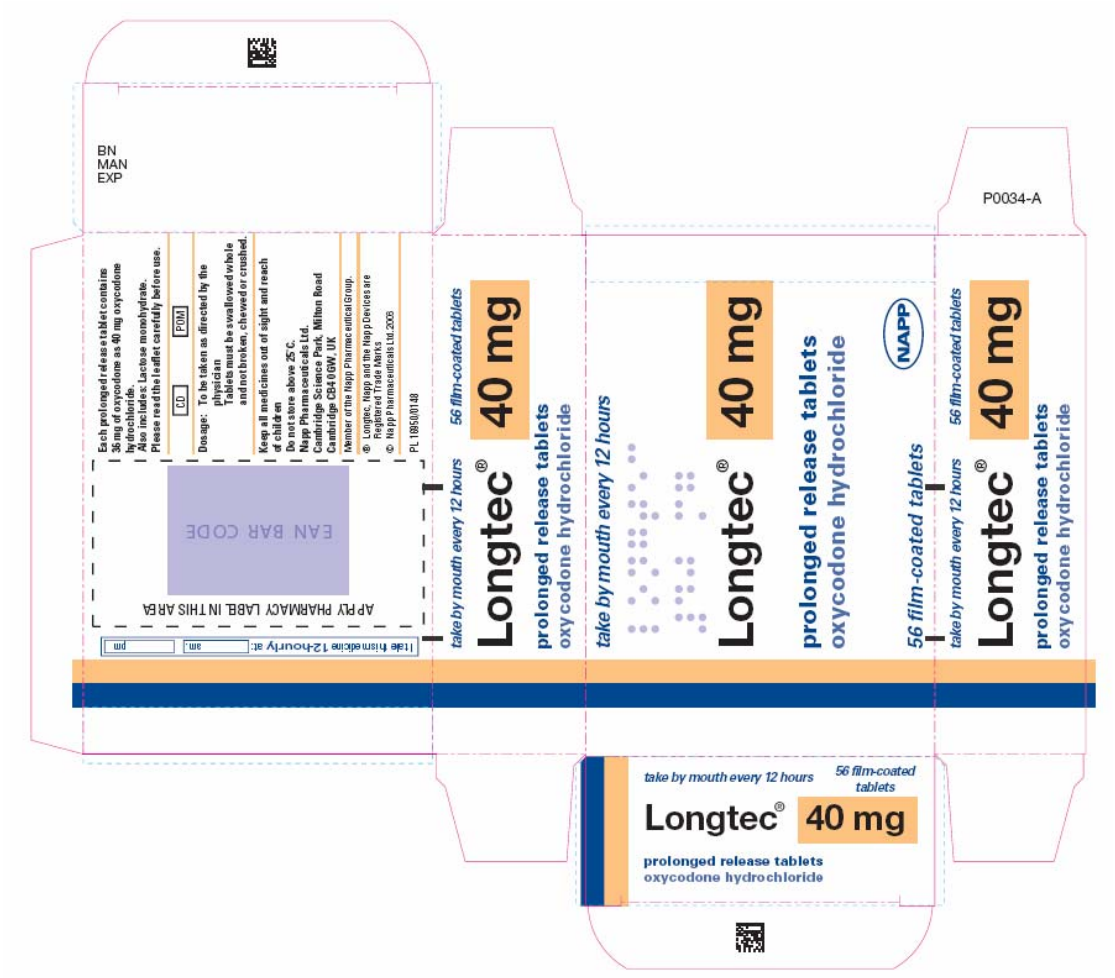

Longtec®
20 mg Prolonged Release Tablets
OXYCODONE HYDROCHLORIDE
MON AM
MON PM
TUE AM
TUE PM
WED AM
WED PM
THUR AM
THUR PM
FRI AM
FRI PM
SAT AM
SAT PM
SUN AM
SUN PM
NAPP
Napp Pharmaceuticals Ltd.


BN
MAN
EXP
P0034-A
Each prolonged release tablet contains 36 mg of oxycodone as 40 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep all medicines out of sight and reach of children
Do not store above 25°C.
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Cambridge CB4 0GW, UK
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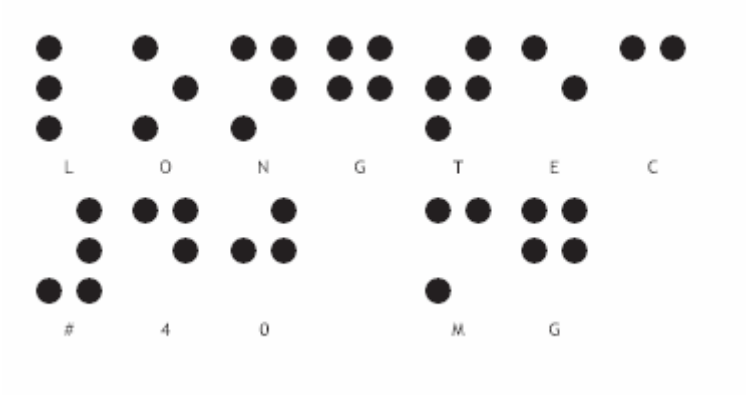
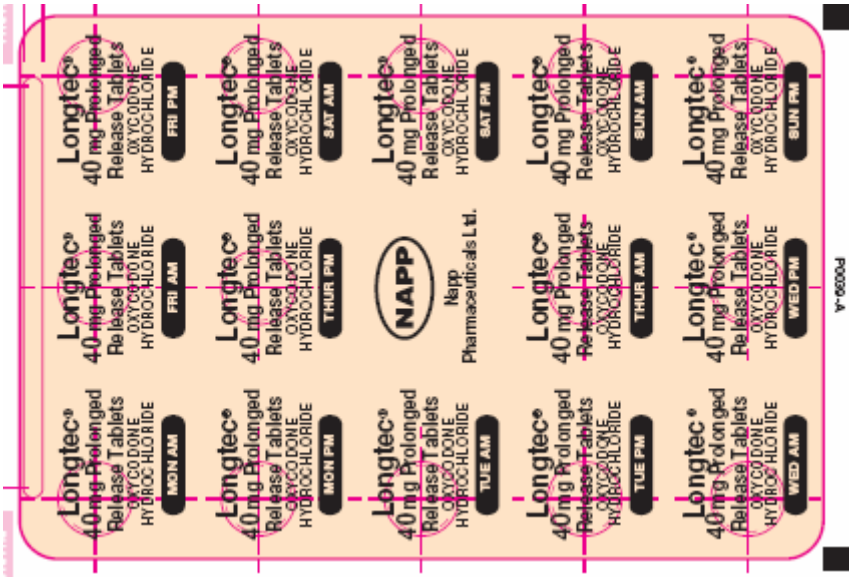
PL 18950/0148
EAN BAR CODE
APPLY PHARMACY LABEL IN THIS AREA
take by mouth every 12 hours
56 film-coated tablets
Longtec® 40 mg
prolonged release tablets
oxycodone hydrochloride
NAPP


L O N G T E C
4 0 M G


Longtec®
40 mg Prolonged Release Tablets
OXYCODONE HYDROCHLORIDE
MON AM
TUE AM
WED AM
THUR AM
FRI AM
SAT AM
SUN AM
MON PM
TUE PM
WED PM
THUR PM
FRI PM
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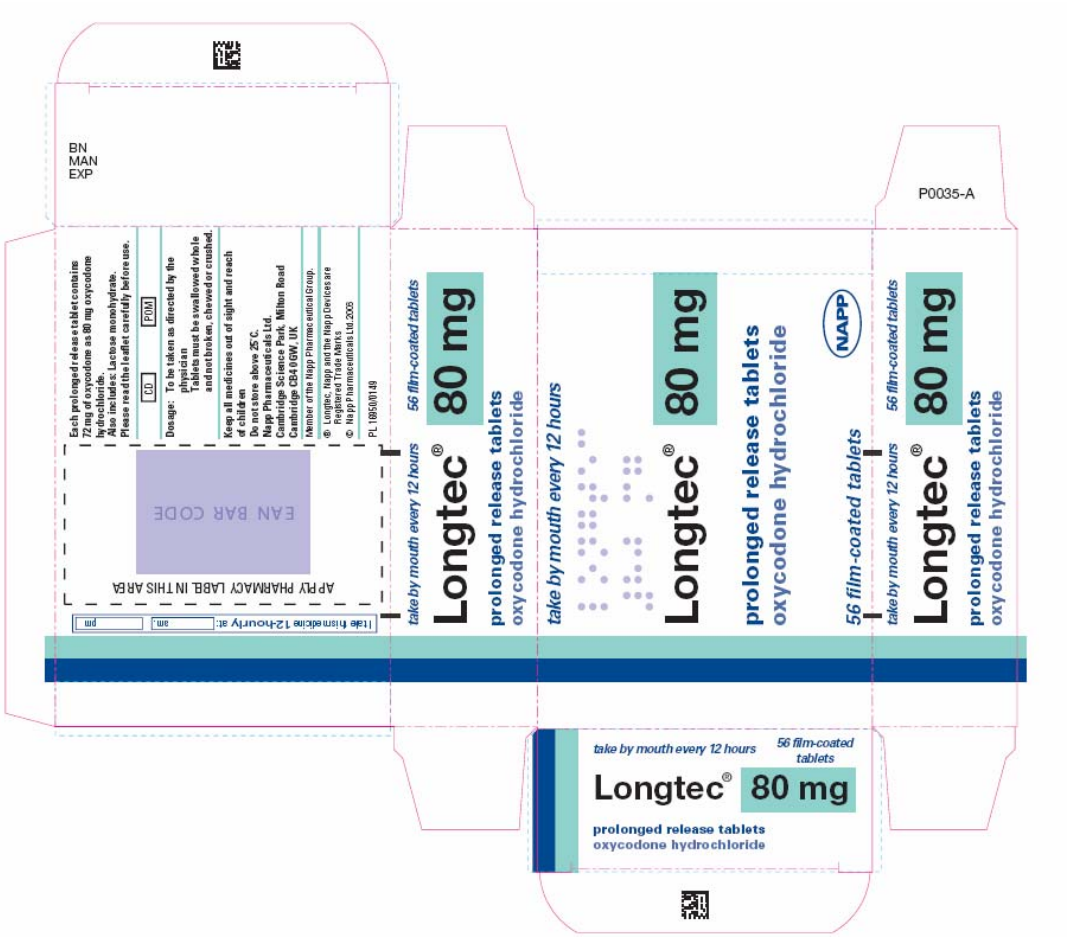
SUN PM
NAPP
Napp Pharmaceuticals Ltd.
P0099-A


BN
MAN
EXP
P0035-A
Each prolonged release tablet contains 72 mg of oxycodone as 80 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep all medicines out of sight and reach of children
Do not store above 25°C.
Napp Pharmaceuticals Ltd.
Cambridge Science Park, Milton Road
Cambridge CB4 0GW, UK
Member of the Napp Pharmaceutical Group.
® Longtec, Napp and the Napp Devices are Registered Trade Marks
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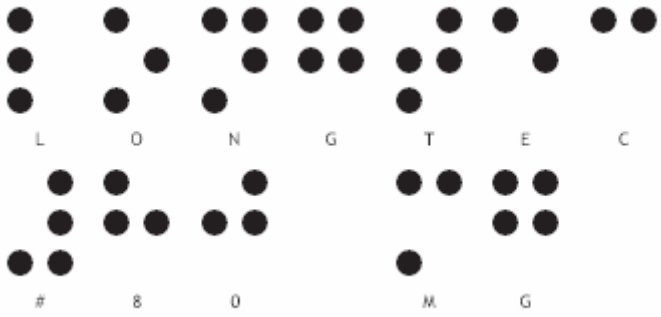
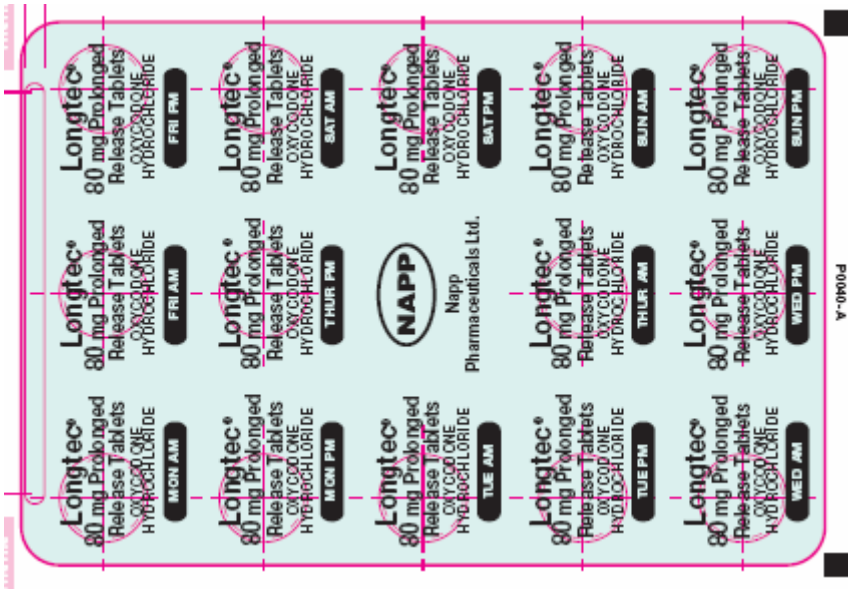
PL 16950/0149
APPLY PHARMACY LABEL IN THIS AREA
EAN BAR CODE
Take thismedicine 12-hourly at:
am
pm
take by mouth every 12 hours
56 film-coated tablets
Longtec®
80 mg
prolonged release tablets
oxycodone hydrochloride
NAPP


L O N G T E C
8 0 M G


Longtec®
80 mg Prolonged Release Tablets
OXYCODONE HYDROCHLORIDE
MON AM
TUE AM
WED AM
THUR AM
FRI AM
SAT AM
SUN AM
MON PM
TUE PM
WED PM
THUR PM
FRI PM
SAT PM
SUN PM
NAPP
Napp Pharmaceuticals Ltd.
P0040-A