Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zeropan Prolonged Release Tablets 40mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

40 mg tablet contain 36.0 mg of oxycodone as 40 m of oxycodone hydrochloride.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release, round, convex tablets.

The 40 mg tablets are yellow, marked "OC" on one side and "40" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of severe pain.

4.2 Posology and method of adminstration

Zeropan tablets must be swallowed whole and are not to be broken, chewed or crushed. Taking broken, chewed or crushed Zeropan tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone.

Adults and the elderly:
Zeropan tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, the patient's previous history of analgesic requirements, the patient's body weight, and sex (higher plasma concentrations are produced in females).

The usual starting dose for debilitated elderly patients, opioid naïve patients or patients presenting with severe pain uncontrolled with weaker opioids is 10 mg 12-hourly. The dose should then be carefully titrated, every day if necessary, to achieve pain relief. Increases should be made, where possible, in 25% - 50% increments. The correct dosage for any individual patient is that which controls the pain and is well tolerated, for a full 12 hours. The need for escape medication more than twice a day indicates that the dosage of Zeropan tablets should be increased.

Conversion from oral morphine:
Patients receiving oral morphine before Zeropan therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine.

It must be emphasised that this is a guide to the dose of Zeropan tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Elderly patients:
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.

Non-malignant pain:
Treatment with Zeropan should be short and intermittent to minimise the risk of dependence. The need for continued treatment should be assessed at regular intervals. Patients should not usually require more than 160 mg per day.

Cancer-related pain:
Patients should be titrated up to a dose which achieves pain relief unless unmanageable adverse drug reactions prevent this.

Patients with renal or hepatic impairment:
Unlike morphine preparations, the administration of Zeropan tablets does not result in significant levels of active metabolites. However, the plasma concentration of oxycodone in this patient population may be increased compared with patients having normal renal or hepatic function. Therefore dose initiation should follow a conservative approach in these patients, i.e. one-third to one half the usual dose with careful dose titration. In severe hepatic impairment, the dosing frequency may also need to be reduced. There are no data on the use of Zeropan in patients undergoing haemodialysis.

Adults under 20 years and children:
Not recommended.

4.3 Contraindications

Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, severe obstructive airways disease, severe bronchial asthma, hypercarbia, known sensitivity to oxycodone, morphine or other opioids, acute hepatic disease, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. The safety of Zeropan used pre-operatively and for up to 24 hours post-operatively has not been established and cannot be recommended.

4.4 Special warnings and precautions for use

As with all narcotics, a reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid dependent patients, patients with toxic psychosis and in patients with raised intracranial pressure, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, chronic renal and hepatic disease, and debilitated patients. Zeropan tablets should not be used where there is a possibility of paralytic ileus occurring. Zeropan 80mg tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Should paralytic ileus be suspected or occur during use, Zeropan 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 Zeropan tablets for 24 hours before surgery. If further treatment with Zeropan tablets is then indicated the dosage should be adjusted to the new post-operative requirement.

As with all opioid preparations, Zeropan 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.

Physical dependence may occur in patients treated with oxycodone. Abrupt withdrawal of the drug or administration of an opioid antagonist may result in an abstinence syndrome. When patients no longer require therapy with Zeropan tablets, patients requiring doses of 20-60 mg/day can usually have therapy stopped abruptly without incident. Higher doses should be reduced over several days, such that the daily dose is reduced by approximately 50% for the first two days, and then reduced by 25% every two days thereafter until the total daily dose reaches the dose recommended for opioid naïve patients, i.e. 10 mg 12 hourly. Therapy can then be discontinued.

Zeropan tablets 80 mg are for use only in opioid-tolerant patients requiring daily oxycodone dosages of 160 mg or more. Care should be taken in the prescription of this tablet strength.

The tablets contain 35.25mg of lactose per tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Zeropan should be used with caution and the dosage reduced in patients using central nervous system depressants as opioids potentiate the effects of phenothiazines, tricyclic anti-depressants, anaesthetics, hypnotics, sedatives, alcohol, muscle relaxants and antihypertensives. Monoamine oxidase inhibitors are known to interact with narcotic analgesics, producing CNS excitation or depression with hyper- or hypotensive crisis.

Oxycodone is metabolised by the cytochrome P450 enzyme system but a full evaluation of interactions with other drugs metabolised by this route has not been undertaken. Concurrent administration of quinidine, an inhibitor of cytochrome P450-2D6, resulted in an increase in oxycodone C_{max} by 11%, AUC by 13% and $t_{1/2}$ elimination by 14%; also an increase in noroxycodone level was observed. The pharmacodynamic effects of Zeropan were not altered. This interaction may be observed for other potent inhibitors of the cytochrome P450-2D6 enzyme. Cimetidine and inhibitors or substrates of cytochrome P450-3A4 such as ketoconazole and erythromycin may inhibit the metabolism of oxycodone.

4.6 Pregnancy and lactation

Zeropan tablets are not recommended for use in pregnancy.

Oxycodone is secreted in breast milk and may cause respiratory depression in the newborn. Zeropan 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. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and constipation, both occurring in approximately 25 to 30% of patients. If nausea or vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation should be anticipated as with any strong opioid, and treated appropriately with laxatives. Should opioid related adverse events persist, they should be investigated for an alternative cause.

Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time, with the exception of constipation. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability.

The most serious adverse reaction as with other opioids, is respiratory depression (see section 4.9 Overdose). This is most likely to occur in elderly, debilitated or opioid-intolerant patients.

Adverse drug reactions seen during clinical trials were:

<u>Very common (>10%):</u>

Digestive: Constipation, vomiting, nausea.

Nervous: Somnolence, dizziness.

Skin and appendages: Pruritus.

<u>Common (1 – 10%):</u>

Body as a whole: Oedema, fever, abdominal pain, asthenia, headache.

Cardiovascular: Vasodilation.

Digestive: Anorexia, diarrhoea, dry mouth, dyspepsia, flatulence.

Nervous: Abnormal dreams, Anxiety, confusion, depression, insomnia, hallucinations, faintness.

Respiratory: Dyspnoea, bronchospasm.

Skin and appendages: Rash, sweating.

Urogenital: Urinary disorders.

Uncommon (0.1 – 1%)

Body as a whole: Chills, chest pain, allergic reaction.

Cardiovascular: Palpitations, syncope.

Digestive: Dysphagia, gastritis, mouth ulceration, eructation, ileus, stomatitis, biliary spasm.

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion.

Metabolism and Nutrition: Dehydration, weight change.

Nervous: Abnormal gait, amnesia, depersonalisation, euphoria, hyperkinesia, hypertonia, hypoaesthesia, hypotonia, speech disorder, stupor, tremor, twitching, vertigo, epileptic seizures, mood changes, paraesthesia, abnormal thinking, withdrawal syndrome, decreased libido.

Respiratory: Rhinitis, epistaxis, hiccup, voice alteration.

Skin and appendages: Dry skin.

Special senses: Lacrimation disorder, abnormal vision, taste perversion, tinnitus, miosis.

Urogenital: Urinary retention, amenorrhoea, impotence.

Tolerance may occur in patients treated with Zeropan, although this has not been a significant problem in the clinical trial programme. Patients requiring marked dose escalation should have their pain control regimen carefully reviewed.

Abrupt withdrawal of Zeropan tablets or administration of an opioid antagonist may result in a withdrawal syndrome characterized by anxiety, irritability, chills, hot flushes, piloerection, joint pain, rhinorrhea, diaphoresis, abdominal cramps and diarrhoea. If the dose reduction regimen recommended in section 4.4 results in withdrawal syndrome, the dose should be slightly increased until the signs and symptoms disappear. Dose reduction should then begin again with longer periods of time between each reduction.

4.9 Overdose

Signs of oxycodone toxicity and overdosage are pin-point pupils and respiratory depression. Respiratory depression may result in apnoea, respiratory arrest, circulatory depression, hypotension, coma or death.

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

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

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

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

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdosage.

Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawals syndrome.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug, particularly when a modified release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Oxycodone is a full opioid agonist with no antagonist properties and has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic and sedative. The precise mechanism of action has not been fully characterised.

5.2 Pharmacokinetic properties

Oxycodone has a high absolute bioavailability of up to 87% following oral administration. It 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 plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from Zeropan 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 Zeropan is 4.5 hours which leads to steady-state being achieved in about one day.

Release of oxycodone from Zeropan tablets is independent of pH.

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

Zeropan 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 Zeropan tablets.

5.3 Preclinical safety data

Oxycodone does not induce abnormalities in rats in doses of up to 8 mg/kg/day or in rabbits in doses of up to 5 mg/kg/day. No fertility, peri-and post-natal studies have been performed. *In-vitro* tests show that oxycodone is potentially clastogenic but there were no such findings in *in-vivo* studies, even at toxic doses. 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
Povidone
Ammoniomethacrylate polymer dispersion
Sorbic acid
Triacetin
Stearyl Alcohol
Talc
Magnesium Stearate
Hypromellose (E464)
Macrogol
Titanium dioxide (E171)
Polysorbate 80
Iron Oxide (E172)

6.2 Incompatibilities

None known.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

1) Polypropylene containers with polyethylene lids (containing 28, 56 or 112 tablets).

2) PVC blister packs with aluminium foil backing (containing 10, 28, 30, 56, or 112 tablets).

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

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CB4 0GW
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8 MARKETING AUTHORISATION NUMBER

PA 913/23/3

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