OXYCODONE HYDROCHLORIDE

Core Safety Profile

4.2 Posology and method of administration (safety aspects only)

Posology

Elderly patients
For oral preparations
A dose adjustment is not usually necessary in elderly patients.
For parenteral preparations
The lowest dose should be administered with careful titration to pain control.

Patients with renal or hepatic impairment
The dose initiation should follow a conservative approach in these patients. The recommended adult starting dose should be reduced by 50% (for example a total daily dose of 10 mg orally in opioid naïve patients), and each patient should be titrated to adequate pain control according to their clinical situation.

Duration of treatment
Oxycodone should not be used for longer than necessary.

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

4.3 Contraindications
Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.

Oxycodone must not be used in any situation where opioids are contraindicated: severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, or paralytic ileus.

4.4 Special warnings and precautions for use
The major risk of opioid excess is respiratory depression. Caution must be exercised when administering oxycodone to the debilitated elderly; patients with severely impaired pulmonary function, impaired hepatic or renal function; patients with myxedema, hypothyroidism, Addison's disease, toxic psychosis, prostate hypertrophy, adrenocortical insufficiency,
alcoholism, delirium tremens, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, hypotension, hypovolaemia, head injury (due to risk of increased intracranial pressure) or patients taking MAO inhibitors.

As with all opioid preparations, oxycodone products 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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. Prolonged use of this product [preparation] 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. Withdrawal symptoms may include yawning, mydriasis, lacrimation, rhinorrhoea, tremor, hyperhidrosis, anxiety, agitation, convulsions and insomnia.

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

Oxycodone has an abuse profile similar to other strong agonist opioids. Oxycodone may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence [addiction] to opioid analgesics, including oxycodone. {(Invented)name} should be used with particular care in patients with a history of alcohol and drug abuse.

The prolonged release tablets must be swallowed whole, and not broken, chewed or crushed. The administration of broken, chewed or crushed controlled release oxycodone tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Concomitant use of alcohol and {(Invented)name} may increase the undesirable effects of {(Invented)name}; concomitant use should be avoided.

For prolonged release products:

{(Invented)name} is not recommended for pre-operative use or within the first 12-24 hours post-operatively.[1]

For normal / immediate release products (oral):

{(Invented)name} should be used with caution pre-operatively and within the first 12-24 hours post-operatively.

For normal / immediate release products (parenteral):
{(Invented)name} should be used with caution pre- or intra-operatively and within the first 12-24 hours post-operatively.

4.5 Interaction with other medicinal products and other forms of interaction

There can be an enhanced CNS depressant effect during concomitant therapy with drugs which affect the CNS such as other opioids, sedatives, hypnotics, anti-depressants, phenothiazines and neuroleptic drugs. MAO-inhibitors are known to interact with narcotic analgesics. MAO-inhibitors causes CNS-excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be used with caution in patients administered MAO-inhibitors or who have received MAO-inhibitors during the last two weeks (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of {(Invented)name}, concomitant use should be avoided.

Oxycodone is metabolised mainly by CYP3A4, with a contribution from CYP2D6. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs or dietary elements.

CYP3A4 inhibitors, such as macrolide antibiotics (e.g. clarithromycin, erythromycin and telithromycin), azol-antifungals (e.g. ketoconazole, voriconazole, itraconazole, and posaconazole), protease inhibitors (e.g. boceprevir, ritonavir, indinavir, nelfinavir and saquinavir), cimetidine and grapefruit juice may cause a reduced clearance of oxycodone that could cause an increase of the plasma concentrations of oxycodone. Therefore the oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- Itraconazole, a potent CYP3A4 inhibitor, administered 200 mg orally for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 2.4 times higher (range 1.5 - 3.4).

- Voriconazole, a CYP3A4 inhibitor, administered 200 mg twice-daily for four days (400 mg given as first two doses), increased the AUC of oral oxycodone. On average, the AUC was approximately 3.6 times higher (range 2.7 - 5.6).

- Telithromycin, a CYP3A4 inhibitor, administered 800 mg orally for four days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.8 times higher (range 1.3 – 2.3).

- Grapefruit Juice, a CYP3A4 inhibitor, administered as 200 ml three times a day for five days, increased the AUC of oral oxycodone. On average, the AUC was approximately 1.7 times higher (range 1.1 – 2.1).

CYP3A4 inducers, such as rifampicin, carbamazepin, phenytoin and St John´s Wort may induce the metabolism of oxycodone and cause an increased clearance of oxycodone that could cause a reduction of the plasma concentrations of oxycodone. The oxycodone dose may need to be adjusted accordingly.

Some specific examples are provided below:

- St Johns Wort, a CYP3A4 inducer, administered as 300 mg three times a day for fifteen days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 50% lower (range 37-57%).

- Rifampicin, a CYP3A4 inducer, administered as 600 mg once-daily for seven days, reduced the AUC of oral oxycodone. On average, the AUC was approximately 86% lower

Drugs that inhibit CYP2D6 activity, such as paroxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

4.6 Fertility, pregnancy and lactation

Use of this medicinal product should be avoided to the extent possible in patients who are pregnant or lactating.

Pregnancy

There are limited data from the use of oxycodone in pregnant women. Infants born to mothers who have received opioids during the last 3 to 4 weeks before giving birth

should be monitored for respiratory depression. Withdrawal symptoms may be observed in the newborn of mothers undergoing treatment with oxycodone

Breastfeeding
Oxycodone may be secreted in breast milk and may cause respiratory depression in the newborn. Oxycodone should, therefore, not be used in breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.

4.8 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
Very common	≥ 1/10
Common	≥ 1/100 to <1/10
Uncommon	≥ 1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Frequency unknown	Cannot be estimated from the available data

Immune system disorders:
Uncommon: hypersensitivity.
Frequency unknown: anaphylactic responses.

Metabolism and nutrition disorders:
Common: decreased appetite.
Uncommon): dehydration.

Psychiatric disorders:
Common: anxiety, confusional state, depression, insomnia, nervousness. abnormal thinking
Uncommon: agitation, affect lability, euphoric mood, hallucinations, decreased libido, drug dependence (see section 4.4).
Frequency unknown: aggression.

Nervous system disorders:
Very common: somnolence, dizziness, headache.
Common: tremor.
Uncommon: amnesia, convulsion, hypertonia, hypoaesthesia, involuntary muscle contractions, speech disorder, syncope, paraesthesia, dysgeusia.
Frequency unknown: hyperalgesia.

Eye disorders:
Uncommon: visual impairment, miosis.

Ear and labyrinth disorders:
Uncommon: vertigo.

Cardiac disorders:
Uncommon): palpitations (in the context of withdrawal syndrome).

Vascular disorders:
Uncommon: vasodilatation.
Rare: hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea.
Uncommon: respiratory depression.

Gastrointestinal disorders:
Very common: constipation, nausea, vomiting.
Common: abdominal pain, diarrhoea, dry mouth, dyspepsia.
Uncommon: dysphagia, flatulence, eructation, ileus.
Frequency unknown: dental caries.

Hepato-biliary disorders:
Uncommon: increased hepatic enzymes.
Frequency unknown: cholestasis, biliary colic.

Skin and subcutaneous tissue disorders:
Very common: pruritus.
Common: rash, hyperhidrosis.
Uncommon: dry skin.
Rare: urticaria.

Renal and urinary disorders:
Uncommon: urinary retention.

Reproductive system and breast disorders:
Uncommon: erectile dysfunction.
Frequency unknown: amenorrhoea.

General disorders and administration site conditions:
Common: asthenic conditions.
Uncommon: chills, drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance. thirst.

4.9 Overdose

Acute overdose with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, and death.

A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed.