SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Abtard 30 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abtard 30 mg prolonged-release tablets:
Each prolonged-release tablet contains 30 mg oxycodone hydrochloride corresponding to 27 mg of oxycodone.

Excipient with known effect:
The prolonged-release tablets contain lactose monohydrate.

Abtard 30 mg prolonged-release tablets:
Each prolonged-release tablet contains 63.2 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Abtard 30 mg prolonged-release tablets:
Brown, round, biconvex tablets, 9 mm in diameter, with ‘OX 30’ debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain, which can be adequately managed only with opioid analgesics.

Abtard is indicated in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Posology

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with oxycodone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

The dosage depends on the intensity of pain and the patient's individual susceptibility to the treatment. The following general dosage recommendations apply:

Adults and adolescents 12 years of age and older

Dose titration and adjustment

In general, the initial dose for opioid naïve patients is 10 mg oxycodone hydrochloride given at intervals of 12 hours. Some patients may benefit from a starting dose of 5 mg to minimize the incidence of side effects.

Patients already receiving opioids may start treatment with higher dosages taking into account their experience with former opioid therapies.

For doses not realisable/practicable with these strengths, other strengths are available.

According to well-controlled clinical studies 10-13 mg oxycodone hydrochloride correspond to approximately 20 mg morphine sulphate, both in the prolonged-release formulation.

Because of individual differences in sensitivity for different opioids, it is recommended that patients should start conservatively with Abtard prolonged-release tablets after conversion from other opioids, with 50-75% of the calculated oxycodone dose.

Some patients who take Abtard prolonged-release tablets following a fixed schedule need rapid release analgesics as rescue medication in order to control breakthrough pain. Abtard prolonged-release tablets are not indicated for the treatment of acute pain and/or breakthrough pain. The single dose of the rescue medication should amount to 1/6 of the equianalgesic daily dose of Abtard prolonged-release tablets. Use of the rescue medication more than twice daily indicates that the dose of Abtard prolonged-release tablets needs to be increased. The dose should not be adjusted more often than once every 1-2 days until a stable twice daily administration has been achieved.

Following a dose increase from 10 mg to 20 mg taken every 12 hours dose adjustments should be made in steps of approximately one third of the daily dose. The aim is a patient-specific dosage which, with twice daily administration, allows for adequate analgesia with tolerable undesirable effects and as little rescue medication as possible as long as pain therapy is needed.

Even distribution (the same dose mornings and evenings) following a fixed schedule (every 12 hours) is appropriate for the majority of the patients. For some patients it may be advantageous to distribute the doses unevenly. In general, the lowest effective analgesic dose should be chosen. For the treatment of non- malignant pain a daily dose of 40 mg is generally sufficient; but higher dosages may be necessary. Patients with cancer-related pain may require dosages of 80 to 120 mg, which in individual cases can be increased to up to 400 mg. If even higher doses are required, the dose should be decided individual balancing efficacy with the tolerance and risk of undesirable effects.

Special attention is required with a view to treating the adverse effects of opioids.

Abtard prolonged-release tablets should be taken twice daily based on a fixed schedule at the dosage determined.

The prolonged-release tablets may be taken with or independent of meals with a sufficient amount of liquid. Abtard prolonged release tablets must be swallowed whole and not broken, chewed or crushed.

Duration of administration

Abtard prolonged-release tablets should not be taken longer than necessary. If long-term treatment is necessary due to the type and severity of the illness careful and regular monitoring is required to determine whether and to what extent treatment should be continued.

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.

Paediatric population

There have been no studies in patients under 12 years of age, therefore oxycodone hydrochloride should not be used in patients under 12 years.

Elderly patients

A dose adjustment is not usually necessary in elderly patients.

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 (see also section 4.3, 4.4 and 5.2).

Risk patients

Risk patients, for example patients with low body weight or slow metabolism of medicinal products, should initially receive half the recommended adult dose if they are opioid naïve. Dose titration should be performed in accordance with the individual clinical situation.

For instructions how to open the child resistant blisters, see section 6.6.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to oxycodone or to any of the excipients listed in section 6.1.
- Severe respiratory depression with hypoxia and/or hypercapnia.
- Severe chronic obstructive pulmonary disease (COPD).
- Cor pulmonale.
- Severe bronchial asthma.
- Elevated carbon dioxide levels in the blood.
- Paralytic ileus.
- Acute abdomen, delayed gastric emptying.

4.4 Special warnings and precautions for use

Paediatric population

Abtard prolonged-release tablets have not been studied in children younger than 12 years of age. The safety and efficacy of the tablets have not been demonstrated and the use in children younger than 12 years of age is therefore not recommended.

Elderly or debilitated patients

The major risk of opioid excess is respiratory depression. Caution is required in elderly or debilitated patients, in patients with severe impairment of lung, liver or kidney function, myxoedema, hypothyroidism, Addison's disease (adrenal insufficiency), intoxication psychosis (e.g. alcohol), prostatic hypertrophy, adrenocortical insufficiency, alcoholism, known opioid dependence, delirium tremens, pancreatitis, diseases of the biliary tract, inflammatory bowel disorders, biliary or ureteric colic, hypotension, hypovolaemia, conditions with increased brain pressure such as head injury, disturbances of circulatory regulation, epilepsy or seizure tendency and in patients taking benzodiazepines or MAO inhibitors.

This medicinal product can suppress the cough reflex.

Patients undergoing abdominal surgery

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.

Patients with severe hepatic impairment should be closely monitored.

Respiratory depression

Respiratory depression is the most significant risk induced by opioids and is most likely to occur in elderly or debilitated patients. The respiratory depressant effect of oxycodone can lead to increased carbon dioxide concentrations in blood and hence in cerebrospinal fluid. In predisposed patients opioids can cause severe decrease in blood pressure.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Endocrine system

Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with oxycodone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Pre-operative use

Abtard prolonged release tablets are not recommended for pre-operative use or within the first 12-24 hours post operatively.

Abusive parenteral venous injection

In case of abusive parenteral venous injection the tablet excipients may lead to necrosis of the local tissue, infection, increased risk of endocarditis, and valvular heart injury which may be fatal, granulomas of the lung or other serious, potentially fatal events.

Tablets must not be chewed or crushed

To avoid damage to the controlled release properties of the tablets 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 rapid release and absorption of a potentially fatal dose of oxycodone (see section 4.9).

Alcohol

Concomitant use of alcohol and oxycodone hydrochloride prolonged-release tablets may increase the undesirable effects of oxycodone hydrochloride; concomitant use should be avoided.

Abtard contains lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of oxycodone and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe oxycodone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation.

In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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, antipsychotics, anaesthetics, muscle relaxants, antihistamines and antiemetics. MAO inhibitors cause CNS excitation or depression associated with hypertensive or hypotensive crisis (see section 4.4). Oxycodone should be administered conservatively to patients who take MAO inhibitors or who have taken MAO inhibitors within the last two weeks (see section 4.4).

Alcohol may enhance the pharmacodynamic effects of oxycodone; concomitant use should be avoided (see section 4.4).

Concomitant administration of oxycodone with anticholinergics or medicines with anticholinergic activity (e.g. tricyclic anti-depressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Cimetidine can inhibit the metabolism of oxycodone.

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, fluoxetine and quinidine, may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.

The effect of other relevant isoenzyme inhibitors on the metabolism of oxycodone is not known. Potential interactions should be taken into account.
Clinically relevant changes in International Normalized Ratio (INR) in both directions have been observed in individuals if coumarin anticoagulants are co-applied with oxycodone hydrochloride.

There are no studies investigating the effect of oxycodone on CYP catalysed metabolism of other drugs.

Concomitant administration of oxycodone with serotonin agents, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) may cause serotonin toxicity. The symptoms of serotonin toxicity may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). Oxycodone should be used with caution and the dosage may need to be reduced in patients using these medications.

4.6 Fertility, pregnancy and lactation

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast feeding

Administration to nursing women is not recommended as oxycodone may be secreted in breast milk and may cause respiratory depression in the infant

4.7 Effects on ability to drive and use machines

Oxycodone may impair the ability to drive and use machines.

With stable therapy, a general ban on driving a vehicle is not necessary. The treating physician must assess the individual situation.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

4.8 Undesirable effects

The commonest undesirable effects of taking oxycodone are nausea and constipation. Both effects are seen in approximately 25-30% of patients following oral administration. If nausea and vomiting are troublesome, oxycodone may be combined with an anti-emetic. As with other potent opioids, constipation is to be expected. Constipation may be prevented with a laxative. If the opioid-related symptoms persist, the physician should investigate whether the cause lies elsewhere.

Except for constipation, the undesirable effects of full opioid agonists tend to wear off as treatment continues. Notifying the patient of the need to expect adverse effects often makes the adverse effects easier to cope with.

As with other opioids, the most serious undesirable effect is respiratory depression (see also section 4.9). Respiratory depression is more likely in elderly, debilitated or opioid- intolerant patients.

The sedative effect usually wears off within a few days. Biliary and ureteral spasms may be observed in patients predisposed to these.

Dependency and tolerance are as a rule not problematic in the treatment of severe pain.

Clinical studies Common – Very common (>1/100) Rare (≥1/10,000 to <1/1,000)	 Increased ADH secretion Weight gain/loss
Cardiac: Uncommon (≥1/1,000 to <1/100)	 Palpitations (in connection with withdrawal symptoms)
Nervous system: 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) Not known	 Somnolence, headache, sedation, dizziness Weakness, tremor, lethargy Amnesia, convulsion, hypertonia, cramps, involuntary muscle contractions, speech disorder, syncope, hypoæsthesia, paræsthesia. Epileptic fits, especially in epileptics or patients with a history of convulsions. Hyperalgesia
Eyes: Common – Very common (>1/100)	 Miosis

Uncommon (≥1/1,000 to <1/100)	Impaired vision, visual disturbances
Ear and labyrinth Uncommon (≥1/1,000 to <1/100)	Vertigo
Respiratory tract, thorax and mediastinum Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Dyspnoea Respiratory depression, bronchospasm
Gastro-intestinal tract Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Not known	Constipation, nausea, vomiting Abdominal pain, diarrhoea, dyspepsia, dry mouth. Dysphagia, ileus, eructation, gastrointestinal disturbance, flatulence Dental caries
Renal and urinary tracts Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Urinary retention, ureteral spasm Hæmaturia
Skin and subcutaneous tissue Very common (≥1/10) Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Pruritus Rash, hyperhidrosis Dry skin, urticaria
Metabolism and nutrition Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Decreased appetite Dehydration
Vascular system Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	 Vasodilatation, orthostatic hypotension Hypotension
General disorders and administration site conditions: Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Not known	 Asthenia, fatigue, hyperhidrosis, shivering Drug withdrawal syndrome, malaise, oedema, peripheral oedema, drug tolerance, thirst Drug withdrawal syndrome neonatal
Immune system Rare (≥1/10,000 to <1/1,000) Not known	 Hypersensitivity Anaphylactoid reaction, anaphylactic reaction
Hepato and biliary tracts Uncommon (≥1/1,000 to <1/100)	Increased hepatic enzymes, biliary spasms

Not known	Biliary colic, cholestasis
Reproductive system and mammae	
Uncommon (≥1/1,000 to <1/100)	Erectile dysfunction, hypogonadism
Not known	Amenorrhoea
Psychiatric disorders	
Common (≥1/100 to <1/10)	Psychiatric effects, such as mood changes (anxiety, depression), euphoria, agitation (normal suppression, spontaneous excitement), confusion, insomnia, nervousness, abnormal thinking
Uncommon (≥1/1,000 to <1/100)	Agitation, affect lability, dysphoria, decreased libido, hallucinations, drug withdrawal (see section 4.4).
Not known	Aggression, drug dependence (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms

The symptoms of acute overdose with oxycodone are respiratory depression, somnolence progressing to stupor or coma, hypotonia, miosis, bradycardia, hypotension, pulmonary oedema and death.

Treatment

Establish patent airway. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose. Other supportive measures should be employed as needed. Maintain and support respiratory and circulatory functions.

In critical cases, 0.8 mg naloxone should be administered intravenously. Repeat at 2-3-minute intervals, if required. Alternatively, administer 2 mg in 500 ml isotonic saline solution or 5% glucose (0.004 mg/ml).

The infusion should be administered at a tempo related to previously administered bolus doses and according to the patient’s response.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. The patient should remain under observation for a further 24-48 hours.

For less severe overdose, 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 overdose.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids
ATC-Code: N02A A05

Oxycodone shows an affinity to kappa, mu and delta opioid receptors in the brain and spinal cord. Similar to morphine in its action. It acts at these receptors as an opioid agonist without an antagonistic effect. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. Compared to rapid-release oxycodone, given alone or in combination with other substances, the prolonged-release tablets provide pain relief for a markedly longer period without increased occurrence of undesirable effects.

5.2 Pharmacokinetic properties

Trials conducted with healthy trial subjects and with patients show predicted correlation between the dosage of oxycodone and plasma concentrations, and between plasma concentrations and certain predictable opioid effects. These last include contracted pupils, sedation and customary medicinal effects on healthy trial subjects, analgesia and a sense of relaxation in patients.

In common with all opioids, the lowest effective plasma concentration varies from patient to patient, especially for patients previously treated with potent opioid agonists. This means that patients must be titrated individually in order to achieve the desired effect.

Abtard prolonged release tablets release the active substance more slowly than instant release oxycodone products.

The in vitro release is independent of pH.

The ingestion of food has no or minimal effect on absorption of the prolonged release tablets.

Biphasic absorption of oxycodone from prolonged release tablets occurs at constant rates of absorption 1.11 hour and 0.11 hour. Maximum plasma concentration is achieved after 3

hours.

The mean apparent elimination half-life of Abtard is 4.5 hours. Mean absolute oral bioavailability of Abtard is reported to be as much as 87%. Oxycodone appears to be absorbed most in older females and least in young males.

Following absorption, oxycodone is distributed throughout the body. About 45% is bound to plasma protein. Distribution volume at steady state is 2.61 l/kg. The substance passes the placenta and may be found in breast milk.

Oxycodone undergoes N-demethylation to noroxycodone and O-demethylation to oxymorphone in the liver. Noroxycodone is then metabolised to noroxymorphone, which is subsequently glucuronidated. CYP3A4 is the primary enzyme responsible for the creation of noroxycodone and noroxymorphone, whereas CYP2D6 is the primary enzyme responsible for the creation of oxymorphone. Tests have proven that urine metabolites from CYP3A N-demethylation of oxycodone amounted to 45% ± 21% of the dosage, while those from CYP2D6 O-demethylation amounted to 11% ± 6% of the dosage. In-vitro drug-drug interaction studies with noroxymorphone in human hepatic microcosms showed no significant inhibition of the activities of CYP2D6 and CYP3A4, which indicates that noroxymorphone has no effect on the metabolism of other medicinal products metabolised via CYP2D6 and CYP3A4. Noroxymorphone binds to mu opioid receptors. Although oxymorphone is shown to be active, the analgesic effect of the metabolites is assumed to be clinically insignificant.

The active substance and its metabolites are secreted in urine and faeces.

Plasma concentrations of oxycodone are barely affected by age, i.e. only 15% higher in the elderly than in the young.

Females have on average 25% higher plasma concentrations compared to me (corrected body weight).

Compared with normal subjects, patients with impaired liver function showed higher plasma concentrations of oxycodone and noroxycodone and lower plasma concentrations of oxymorphone. The elimination half life of oxycodone may increase which may be accompanied by increased potency of the medicinal product.

Compared with normal subjects, patients with impaired kidney function showed higher plasma concentrations of oxycodone and its metabolites. The elimination half life of oxycodone may increase which may be accompanied by increased potency of the medicinal product.

Average values for pharmacokinetic parameters for oxycodone following an initial dose of Abtard prolonged release tablets 20 mg to healthy subjects and to patients with renal or hepatic impairment

	Kidneys			Liver		
	Healthy trial subjects	Impaired kidney function	% change	Healthy trial subjects	Impaired liver function	% change
AUC (ng.t/ml)	249.4	400.8	61	199.3	387.1	94
Cmax (ng/ml)	21.4	30.9	44	16.9	24.8	47
t1/2 elim (t)	4.88	5.81	19	5.41	7.73	43

5.3 Preclinical safety data

Teratogenicity

Oxycodone had no effect on fertility and early embryonic development in male and female rats in doses of up to 8 mg/kg body weight and induced no malformations in rats in doses of up to 8 mg/kg and in rabbits in doses of 125 mg/kg bodyweight. However, in rabbits, when individual foetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals. In a study on pre- and postnatal development in rats F1 body weights were lower at 6 mg/kg/d when compared to body weights of the control group at doses which reduced maternal weight and food intake (NOAEL 2 mg/kg body weight). There were neither effects on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices.

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

Carcinogenicity

Long-term carcinogenicity studies were not performed.

Mutagenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Hypromellose

Povidone K30

Stearic acid

Magnesium stearate

Colloidal anhydrous silica

Tablet coating

Polyvinyl alcohol

Macrogol 3350

Talc

Iron oxide, red (E172)

Iron oxide, black (E172)

Blue Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack:
3 years

HDPE container:
3 years
Once opened use within 6 months

6.4 Special precautions for storage

Blister pack:
Do not store above 25°C.

HDPE container:
This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Child resistant blister packs (PVC/PVdC/Al/PET/paper).

Pack sizes:

5 mg: 1, 20, 28, 30, 50, 56, 60 and 100 prolonged-release tablets

10 mg, 20 mg, 40 mg, 80 mg: 1, 20, 28, 30, 50, 56, 60, 98 and 100 prolonged-release tablets

15 mg: 1, 20, 30, 56, 98 and 100 prolonged-release tablets

30 mg, 60 mg: 1, 20, 30, 50, 56, 98 and 100 prolonged-release tablets

Blister packs (PVC/Al) in cartons.

Pack sizes:

5 mg: 1, 20, 28, 30, 50, 56, 60 and 100 prolonged-release tablets

10 mg, 20 mg, 40 mg, 80 mg: 1, 20, 28, 30, 50, 56, 60, 98 and 100 prolonged-release tablets

15 mg: 1, 20, 30, 56, 98 and 100 prolonged-release tablets

30 mg, 60 mg: 1, 20, 30, 50, 56, 98 and 100 prolonged-release tablets

White, round, child-resistant, HDPE tablet containers with PP caps.

Pack size: 98 and 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Instructions for use of child resistant blisters:

1. Do not push the tablet directly out of the pocket
2. Separate one blister cell from the strip at the perforations
3. Carefully peel off the backing to open the pocket

7 MARKETING AUTHORISATION HOLDER

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