SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ZYDOL XL 200 mg prolonged release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of tramadol hydrochloride.

Excipient with known effect:
Each prolonged-release tablet contains 2.00 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet
White, film coated, oval shaped tablets approximately 15 mm in length marked T 200 on one side

4.1. Therapeutic indications

Treatment of moderate to severe pain.

These tablets are indicated in adults and adolescents aged 12 years and above.

4.2 Posology and method of administration

Route of administration
Oral use

Posology
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective correct dose for analgesia should generally be selected. The correct dosage per individual patient is that which controls the pain with no or tolerable side effects for a full 24 hours. Patients transferring from immediate release tramadol preparations should have their total daily dose calculated, and start on the nearest dose in the ZYDOL XL range. It is recommended that patients are slowly titrated to higher doses to

minimise transient side effects. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4). A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

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

Adults and children over 12 years:
The usual initial dose is one 150 mg tablet daily. If pain relief is not achieved, the dosage should be titrated upwards until pain relief is achieved.

Geriatric patients:
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary, it is recommended that a reduced daily dose should be considered.

Renal insufficiency/dialysis and hepatic impairment:
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. Therefore, if necessary, it is recommended that a reduced daily dose should be considered.

As tramadol is only removed very slowly by haemodialysis or by haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Paediatric population under 12 years of age:
ZYDOL XL has not been studied in children. The safety and efficacy of ZYDOL XL has not been established and the product should not be used in children.

Method of administration
These tablets should be taken at 24-hourly intervals and must be swallowed whole and not broken, crushed or chewed.

4.3. Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

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 and 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 tramadol.

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.

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.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Tramadol should be used with caution in patients with head injury, intracranial lesions, increased intracranial pressure, severe impairment of hepatic or renal function, in patients in shock or with a reduced level of consciousness of uncertain origin, and with constipation.

The primary risk of opioid excess is respiratory depression.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs (see section 4.5) are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

Concomitant use of tramadol 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 tramadol 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).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9). If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations. Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion In patients who present with CSA, consider decreasing the total opioid dosage.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold (see section 4.5). Tramadol should therefore be used with caution in patients prone to convulsive disorders.

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

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

Adrenal insufficiency

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Paediatric Population

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

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). Drugs which depress the CNS include but are not limited to: other opioids (including antitussives and substitution therapy), anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, barbiturates and alcohol.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

Simultaneous treatment with carbamazepine may shorten the analgesic effect as a result of a reduction in serum levels of tramadol and its active metabolite.

Co-administration with cimetidine is associated with a small prolongation of the half-life of tramadol, but this is not clinically relevant.

Co-administered ritonavir may increase serum concentrations of tramadol resulting in tramadol toxicity.

Digoxin toxicity has occurred rarely during co-administration of digoxin and tramadol.

Mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine); The analgesic effect of tramadol, which is a pure agonist, may be reduced and a withdrawal syndrome may occur.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of tramadol in pregnant women. Animal studies have shown reproductive toxicity, but not teratogenic effects (see section 5.3). Tramadol crosses the placental barrier. 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. Tramadol administered before or during birth does not affect uterine contractility.

Breastfeeding

Tramadol is secreted in breast milk and may cause respiratory depression in the infant. Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with tramadol. Discontinuation of breastfeeding is generally not necessary following a single dose of tramadol.

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness, blurred vision and dizziness which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

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 you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
    - 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.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected).

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law.

4.8 Undesirable effects

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

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)
Not known (cannot be estimated from the available data)

	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Immune system disorders				Hyper-sensitivity Anaphylactic and anaphylactoid responses		
Metabolism and nutrition disorders				Decreased appetite		Hypoglycaemia
Psychiatric disorders				Hallucinations Nightmare Mood altered Euphoric mood Dysphoria Decreased activity Illusion Confusional state		Drug dependence (see section 4.4)
Nervous system disorders	Dizziness	Somnolence	Headache	Paraesthesia Psychomotor hyperactivity		Sleep apnoea syndrome Hyperalgesia

	Very Common	Common	Uncommon	Rare	Very Rare	Not known
				Cognitive disorder Sensory disturbance Judgement impaired Seizure Syncope		Serotonin syndrome
Eye disorders				Blurred vision		
Cardiac disorders			Palpitations Tachycardia	Bradycardia		
Vascular disorders			Orthostatic hypotension Hypotension Circulatory collapse	Hypertension Flushing		
Respiratory, thoracic and mediastinal disorders				Dyspnoea Worsening of asthma Respiratory depression. Bronchospasm Wheezing		Hiccups
Gastro-intestinal disorders	Nausea	Vomiting Dry mouth	Retching Constipation Abdominal discomfort	Diarrhoea		
Hepatobiliary disorders					Hepatic enzyme increased	
Skin and subcutaneous tissue disorders		Hyperhi-drosis	Pruritus Rash Urticaria	Angioedema		
Musculoskeletal and connective tissue disorders				Muscular weakness		
Renal and urinary disorders				Micturition disorders Dysuria Urinary retention		
General disorders and administration site conditions			Drug Withdrawal syndrome which may include: • agitation; • anxiety; • nervousness; • insomnia; • hyperkinesia; • tremor; • gastrointestinal symptoms.			Asthenia Drug withdrawal syndrome neonatal Drug tolerance

Paediatric population
Neonatal drug withdrawal syndrome may occur in infants born to mothers taking tramadol, however the frequency is unknown (see section 4.6).

As these tablets are made using an insoluble matrix from which the active ingredient is gradually released, the patient may notice the matrix in their faeces.

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

Symptoms
Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, circulatory collapse, sedation and coma, seizures and respiratory depression. Serotonin syndrome has also been reported. In severe cases tramadol overdose may result in a fatal outcome. 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.

Management
A patent airway must be maintained. The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose induced by tramadol, though it will not antagonise tramadol's inhibitory effects on MAO reuptake or serotonin releasing effects. Other supportive measures should be employed as needed. Naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam. In case of oral intake of overdose, consider activated charcoal if the patient presents within one hour of ingestion of tramadol, provided the patient's airway can be protected.

Although it may seem reasonable to assume that later administration of activated charcoal may be beneficial for prolonged-release preparations and drugs that slow gastric emptying, there is no clinical trial evidence to support this.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesic, Other opioids. ATC code: N02AX02

Mechanism of action
Tramadol is a centrally acting analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and serotonin.

Paediatric population
Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

5.2 Pharmacokinetic properties

Absorption
Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%.

Biotransformation
Tramadol is metabolised to 0-desmethyltramadol, which has been shown to have analgesic activity in rodents. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Elimination
The elimination half life of tramadol is around 6 hours, although this is extended to around 16 hours following prolonged absorption from the ZYDOL XL tablet.

Following administration of one ZYDOL XL tablet 200 mg in the fasting state, a mean peak plasma concentration (Cmax) of 192 ng.ml-1 was attained. This was associated with a median tmax of 6 hours (range 4-8 hours). The availability of tramadol from the ZYDOL XL tablet 200 mg was complete when compared with an immediate release tramadol solution 100 mg, after dose adjustment. In the presence of food, the availability and controlled release properties of ZYDOL XL tablets were maintained, with no evidence of dose-dumping.

A single dose-proportionality study has confirmed a linear pharmacokinetic response (in relation to tramadol and 0-desmethyltramadol) following administration of the 200 mg, 300 mg and 400 mg tablets. A steady state study has confirmed the dose adjusted bioequivalence of the 150 mg and 200 mg tablets administered once-daily. This study also confirmed that the ZYDOL XL tablet 150 mg provided an equivalent peak concentration and extent of availability of tramadol to an immediate release capsule 50 mg administered 8-hourly. On this basis it is recommended that patients receiving immediate release tramadol should be transferred initially to the nearest daily dose of ZYDOL XL tablets. It may be necessary to titrate the dose thereafter.

A further steady state study has demonstrated that immediate release tramadol tablets 50 mg, administered 6-hourly, provided plasma concentrations that were greater than would have been anticipated following administration of a single dose. This observation is consistent with a non-linear elimination of the drug substance. In contrast, the plasma concentrations from ZYDOL XL tablet 200 mg administered once-daily were in line with single dose data, confirming that the controlled delivery of tramadol from ZYDOL XL minimises the non-linearity associated with faster-releasing preparations. The more predictable plasma concentrations may lead to a more manageable dose titration process.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

Reproductive and developmental toxicity

No effects of tramadol have been observed on male or female fertility in rats. Fetal malformations occurred in a rat developmental study in the presence of maternal toxicity and mortality. No developmental effects were observed in the rat at 20 mg/kg/day when plasma concentrations of tramadol and O-desmethyltramadol were 2.1x and 2.0x the estimated mean clinical Cmax and 0.6x and 0.7x the estimated mean clinical AUCt at the maximum recommended dose of ZYDOL XL 400 mg once daily. When female rats were treated during gestation and lactation there was increased pup mortality and decreased body weights during lactation for the offspring at maternally toxic dose levels of 60 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydrogenated vegetable oil

Talc

Magnesium stearate

Film coat

Lactose monohydrate

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol 4000

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC blisters with aluminium backing foil (containing 2, 7 ,14, 28, 30, 56 or 60 tablets).

Polypropylene containers with polyethylene lids (containing 2, 7, 14, 28, 30, 56 or 60 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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CB4 0GW

8 MARKETING AUTHORISATION NUMBER(S)

PL 16950/0090

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10 DATE OF REVISION OF THE TEXT

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