SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zamadol® Capsules 50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zamadol capsule contains 50 mg of tramadol hydrochloride.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and prevention of moderate to severe pain.

4.2 Posology and method of administration

Posology

The dose of Zamadol Capsules 50 mg should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

Dosage for adults and adolescents aged 12 years and older is:

For acute pain - an initial dose of 100 mg is usually necessary. This can be followed by doses of 50 mg or 100 mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.

For pain associated with chronic conditions -use in an initial dose of 50 mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported, although rarely (see section 4.4)

A total oral daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Paediatric population

Zamadol Capsules 50 mg should not be taken by children under 12 years of age, since safety and efficacy have not been established.

Elderly patients:

A dose adjustment is usually necessary in patients up to 75 years of age without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years of age elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Patients with renal or hepatic impairment:

In patients with renal and/or hepatic insufficiency the elimination of Zamadol 50 mg capsules is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

- For creatinine clearance <30 ml/min the dosing should be increased to 12 hourly intervals.
- For creatinine clearance <10 ml/min (severe renal impairment) Zamadol 50 mg capsules is not recommended.

Tramadol is removed very slowly by haemodialysis or haemofiltration and therefore post-dialysis dosing to maintain analgesia is usually unnecessary.

Method of administration

The capsules are to be taken whole with sufficient liquid, independently of meals.

Swallow the capsules whole with some water without chewing.

If you have difficulty in swallowing, you may open the capsules. You must open them very carefully by pulling and twisting each end over a spoon so that all the pellets stay in the spoon. Do not chew. Swallow all the pellets with water.

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).

Treatment goals and discontinuation

Before initiating treatment with Zamadol Capsules 50 mg, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance tramadol hydrochloride or to any of the excipients listed in section 6.1.

- Acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol.

- In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within 2 weeks of their withdrawal.

- Uncontrolled epilepsy.

Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

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.

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

Concomitant use of Zamadol Capsules 50 mg 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 Zamadol Capsules 50 mg 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).

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.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Zamadol Capsules 50 mg. Repeated use of Zamadol Capsules 50 mg can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Zamadol Capsules 50 mg may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Zamadol Capsules 50 mg and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see

section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

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%

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)

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 postoperatively 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.

In patients with severe renal or hepatic impairment, head injury, increased intracranial pressure, or patients in shock or at risk of convulsions, Zamadol Capsules 50 mg should be used with caution.

At present Zamadol Capsules 50 mg should not be used during light planes of anaesthesia as enhanced intra-operative recall was reported in a study of the use of tramadol during anaesthesia with enflurane and nitrous oxide.

At therapeutic doses of tramadol respiratory depression has been reported infrequently. Therefore, care should be taken when administering Zamadol Capsules 50 mg to patients with existing respiratory depression or to patients taking concomitant CNS depressant drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Patients treated with monoamine oxidase inhibitors within 14 days prior to administration of the opioid pethidine have experienced life-threatening interactions affecting the central nervous system as well as the respiratory and circulatory centres. The possibility of similar interactions occurring between monoamine oxidase inhibitors and tramadol cannot be ruled out.
Zamadol Capsules 50 mg may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol) when administered concomitantly with such drugs.

The concomitant use of tramadol with sedative medicines such as benzodiazepines or related drugs including gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effects. The dose and duration of concomitant use should be limited (see section 4.4).
Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other seizure threshold lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions (see section 4.4)
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).
Administration of Zamadol Capsules 50 mg together with carbamazepine results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.
Theoretically, tramadol could interact with noradrenaline, 5-HT or lithium, due to their mechanisms of action, and thus potentiate their anti-depressant effect. However there have been no reports of such interactions.
Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Zamadol Capsules 50 mg should not be used in pregnancy, as there is inadequate evidence available to assess the safety of tramadol in pregnant women.
Studies of tramadol in rats and rabbits have revealed no teratogenic effects. However, embryotoxicity was shown in the form of delayed ossification. Fertility, reproductive performance and development of offspring were unaffected.
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:
Approximately 0.1% of the maternal dose of tramadol may be secreted 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, administration to nursing women is not recommended as tramadol may cause respiratory depression I the infant. Alternatively, breast-feeding should

be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

4.7 Effects on ability to drive and use machines

Zamadol Capsules 50 mg may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Patients should be warned not to 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 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

Gastrointestinal disorders:

Very common (≥1/10): nausea

Common (≥1/100 to <1/10): vomiting, dry mouth and constipation.

Nervous system disorders:

Very common (≥1/10): dizziness

Common (≥1/100 to <1/10): headache and drowsiness

Rare (≥1/10,000 to <1/1,000) syncope, somnolence, and parasthesia have been reported. Epileptiform convulsions have been reported occurring mainly after administration of high doses of tramadol or after treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (e.g. anti-depressants or anti-psychotics).

Not known: Serotonin syndrome

Psychiatric disorders:

Rare (≥1/10,000 to <1/1,000): confusion, hallucinations, dysphoria, nightmares

Frequency not known (cannot be estimated from the available data): Drug dependence (see section 4.4).

General disorders and administration site conditions:

Uncommon (≥1/1,000 to <1/100): drug withdrawal syndrome (withdrawal reactions including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms have been reported) (see sections 4.2 and 4.4)

Rare (≥1/10,000 to <1/1,000): fatigue

Eye disorders:

Rare (≥1/10,000 to <1/1,000): blurred vision

Respiratory, thoracic and mediastinal disorders:

Rare (≥1/10,000 to <1/1,000): respiratory depression

Frequency unknown: Hiccups

Immune system disorders:

Rare (≥1/10,000 to <1/1,000) allergic reactions (dyspnoea, wheezing, bronchospasm and worsening of asthma) and anaphylaxis have been reported.

Cardiac disorders:

Uncommon (≥1/1,000 to <1/100): palpitations, tachycardia

Rare (≥1/10,000 to <1/1,000): bradycardia

Vascular disorders:

Uncommon (≥1/1,000 to <1/100): orthostatic hypotension, flushing

Rare (≥1/10,000 to <1/1,000): hypertension

Metabolism and nutrition disorders:

Frequency not known (cannot be estimated from the available data): hypoglycaemia, hyponatraemia.

Skin and subcutaneous tissue disorders:

Common (≥1/100 to <1/10): sweating

Rare (≥1/10,000 to <1/1,000): Pruritus, urticaria and skin rashes have been reported.

Renal and urinary system disorders:

Rare (≥1/10,000 to <1/1,000): micturition disorders

Blood and lymphatic system disorders:

There have also been cases of blood dyscrasias observed with tramadol treatment, but direct causality has not been confirmed.

Hepatobiliary disorders:

In a few isolated cases increases in liver enzyme values have been reported concurrently with the therapeutic use of tramadol.

Drug dependence

Repeated use of Zamadol Capsules 50 mg can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (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

Symptoms of tramadol overdose include vomiting, miosis, sedation, coma, seizures, cardiovascular collapse and respiratory depression. Such symptoms are typical of opioid analgesics.

Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam.

The treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Analgesic, ATC Code: N02AX02

Tramadol, a cyclohexanol derivative, is a centrally acting analgesic which possesses opioid agonist properties. Tramadol appears to modify the transmission of pain impulses by inhibition of monoamine reuptake. The duration of analgesia with orally administered tramadol has been shown to be 3-6 hours with maximum pain relief at 1-4 hours post-dosing. Tramadol also has an antitussive action but has no effect on gastrointestinal motility. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant.

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 2mg/kg or multiple doses of up to 8mg/kg per day (to a maximum of 400mg 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 that 1 year (see section 4.2).

5.2 Pharmacokinetic properties

a) General

Following oral dosing, tramadol is rapidly and almost completely absorbed. After oral administration as capsules or tablets, tramadol appears in the plasma within 15 - 45 minutes, reaching peak plasma concentrations at a mean of 2 hours. The mean oral bioavailability of tramadol is approximately 68% after single doses and increases to 90 to 100% on multiple administrations.

The half-life absorption for oral tramadol (solid dose formulation) is 0.38 ± 0.18 hours with a peak plasma concentration of 280 ± 49 ng/ml 2 hours after oral dosing with 100 mg tramadol (solid dose formulation). Tramadol has a high tissue affinity with an apparent volume of distribution of 306 litres after oral dosing in healthy volunteers.

Tramadol undergoes hepatic metabolism with approximately 85% of an oral dose being metabolised in young healthy volunteers. Tramadol is biotransformed primarily by N- and O-demethylation and by glucuronidation of the O-demethylation products. Eleven metabolites have so far been identified in man.
Only one metabolite, O-demethyl tramadol (M1), is pharmacologically active showing analgesic activity. The mean elimination half-life of tramadol following oral administration is 5 - 6 hours. Approximately 90% of an oral dose is excreted by the kidneys.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the biotransformation of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

b) Characteristics in patients

Effect of age: Tramadol pharmacokinetics show little age-dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, the terminal elimination half-life was 7.0 ± 1.6 h compared to 6.0 ± 1.5 h in young volunteers after oral administration.

<u>Paediatric population</u>

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.

Effect of hepatic or renal impairment: As both tramadol and its pharmacologically active metabolite, O-demethyl tramadol, are eliminated both metabolically and

renally, the terminal half-life of elimination (t½) may be prolonged in patients with hepatic or renal dysfunction. However, the increase in t½ is relatively small if either excretory organ is functioning normally. In liver cirrhosis patients, the mean t½ of tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the t½ of tramadol was 11.0 ± 3.2 hours and that of M1 was 16.9 ± 3.0 hours. Extreme values observed to date are 22.3 hours (tramadol) and 36.0 hours (M1) in liver cirrhosis patients and 19.5 hours (tramadol) and 43.2 hours (M1) in renal failure patients.

5.3 Preclinical safety data

The standard range of pharmacodynamic, pharmacokinetic and toxicological tests have been carried out for Tramadol and the effects observed from these investigations that are relevant to the prescriber are mentioned in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents: Dibasic calcium phosphate anhydrous, magnesium stearate, colloidal anhydrous silica.

Capsule Shell: Gelatin and Titanium Dioxide (E171).

Printing ink: Shellac, Iron oxide black (E172), propylene glycol and ammonium hydroxide.

6.2 Incompatibilities

No pharmaceutical incompatibilities reported.

6.3 Shelf life

Two years, as packaged for sale.

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

White opaque PVC/PVDC and aluminium foil blister strips. Each strip contains 10 capsules. The blister strips are packed in cartons containing 100 capsules.

6.6 Special precautions for disposal

None.

7. MARKETING AUTHORISATION HOLDER

Viatris Products Limited
20 Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0148

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 August 1996

10 DATE OF REVISION OF THE TEXT

06/11/2025