

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ZERMADOL 50 CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg tramadol hydrochloride

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Gelatin (Capsules).

Green Cap/Green Body Size 2 Hard Gelatin Capsules Containig a white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

Tramadol Capsules is indicated in adults and adolescents aged 12 years and over.

4.2 Posology and method of administration

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).

Posology

The dose 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. The total daily dose of 400 mg active substance should not be exceeded, except in special circumstances.

Unless otherwise prescribed, Tramadol should be administered as follows:

Adults and adolescents aged 12 years and over

Acute Pain: An initial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100mg at 4 - 6 hourly intervals, and duration of treatment should be matched to clinical need (see section 5.1).

Pain Associated with Chronic Conditions: An initial dose of 50mg is advised and then titration according to pain severity. The need for continued treatment should be assessed at

regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4).

Children

Tramadol capsules are not suitable for children below the age of 12 years.

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 the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic impairment

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

Method of administration

For oral administration

The capsules are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Duration of administration

Tramadol should under no circumstances be administered for longer than absolutely necessary. If long term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Treatment goals and discontinuation

Before initiating treatment with Tramadol, 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**

Tramadol is contraindicated in:

- hypersensitivity to tramadol or to any of the excipients, listed in section 6.1;
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal drugs;
- patients who are receiving monoamine oxidase (MAO) inhibitors or have been taking them within the last 14 days (see section 4.5);
- patients with epilepsy not adequately controlled by treatment.
- for use in narcotic withdrawal treatment.

4.4 **Special warnings and precautions for use**

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure. In patients sensitive to opiates the product should only be used with caution.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

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.

Serotonin syndrome is likely when one of the following is observed: Spontaneous clonus

Inducible or ocular clonus with agitation or diaphoresis Tremor and hyperreflexia

Hypertonia and body temperature > 38 °C and inducible or ocular clonus

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.

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 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.

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

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.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (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.

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.

Tolerance, psychic and physical dependence may develop, especially after long term use. In patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

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

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

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%

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.

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

Concomitant use of Tramadol Capsules 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 Capsules concomitantly with sedative medicines, the lowest effective dose of Tramadol should be used, and the duration of concomitant 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).

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 tramadol. Repeated use of tramadol 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 tramadol 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 Tramadol 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.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors (see section 4.3). In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol.

Centrally acting medicinal products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs.

The concomitant use of Tramadol with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (e.g. other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. (see section 4.8).

Therefore, if a decision is made to prescribe Tramadol concomitantly with respiratory or CNS depressants, the lowest effective dose of Tramadol should be used, and the duration of the concomitant treatment should be as short as possible.

The concomitant use of Tramadol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Anticholinergics

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

Concomitant administration of Tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal product (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 section 4.4 and 4.8)

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT₃ antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women.

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.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms. 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 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, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 **Effects on ability to drive and use machines**

Even when taken according to instructions, Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, particularly alcohol.

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

4.8 **Undesirable effects**

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

The frequencies are defined as follows:

- Very common: $\geq 1/10$
- Common: $\geq 1/100$, $< 1/10$
- Uncommon: $\geq 1/1000$, $< 1/100$
- Rare: $\geq 1/10\ 000$, $< 1/1000$
- Very rare: $< 1/10\ 000$
- Not known: cannot be estimated from the available data

System Organ Class	Frequency	Adverse Reactions
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Cardiac disorders	Uncommon	Cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
	Rare	Bradycardia
Investigations	Rare	Increase in blood pressure
Vascular disorders	Uncommon	Cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Metabolism and nutrition disorders	Rare	Changes in appetite
	Not known	Hypoglycaemia
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression, dyspnoea. (If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.). Worsening of asthma has been reported, though a causal relationship has not been established.
	Not known	Hiccups
Nervous system disorders	Very common	Dizziness
	Common	Headache, somnolence
	Rare	Paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders. Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).
	Not known	Serotonin syndrome
Psychiatric disorders	Rare	hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic adverse reactions may occur following

		administration of tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).
	Frequency unknown	Drug dependence (see section 4.4)
Eye disorders	Rare	Miosis, mydriasis, blurred vision
Gastrointestinal disorders	Very common	Nausea
	Common	Constipation, dry mouth, vomiting
	Uncommon	Retching; gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Dermal reactions (e.g. pruritus, rash, urticaria)
Musculoskeletal and connective tissue disorders	Rare	Motorial weakness
Hepatobiliary disorders	Frequency unknown	In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.
Renal and urinary disorders	Rare	Micturition disorders (dysuria and urinary retention)
Immune system disorders	Rare	Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
General disorders and administration site conditions:	Common	Fatigue
	Uncommon	Drug withdrawal syndrome Symptoms of drug withdrawal syndrome,

		similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).
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Drug dependence

Repeated use of Tramadol 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. Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

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

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Serotonin syndrome has also been reported.

Treatment

The general emergency measures apply. Keep open the respiratory tract (aspiration!), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

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.

Overdose

Serotonin syndrome has also been reported.

5.1 Pharmacodynamic properties

Tramadol Hydrochloride 50mg Effervescent Tablets is a centrally acting analgesic. It is non selective pure agonist at mu, delta and kappa opioid with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibitor of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

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

The half life of the terminal elimination phase ($t_{1/2\beta}$) was $6.0 \pm$ h in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, $t_{1/2\beta}$ was 7.0 ± 1.6 on oral administration. Since tramadol is eliminated both metabolically and renally, the terminal half-life $t_{1/2\beta}$ may be prolonged in impaired hepatic or renal function. However, the increase in the $t_{1/2\beta}$ values is relatively if at least one of these organs is functioning normally. In patients with liver cirrhosis $t_{1/2\beta}$ tramadol was a mean of 13.3 ± 4.9 h; inpatients with renal insufficiency (creatinine clearance <5 ml/min) it was 11.0 ± 3.2 h.

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

More than 90% of Tramadol Hydrochloride 50mg Effervescent Tablets is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity ($V_{d,\beta} = 203 + 40$ l). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life $t_{1/2,\beta}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only Odesmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

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.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyiltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dosedependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyiltramadol 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 Odesmethyiltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyiltramadol 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-desmethyiltramadol in children under 1 year of age.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs, haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20mg/kg and 10mg/kg body weight respectively, and dogs rectal doses of 20mg/kg body weight without any reactions.

In rats tramadol dosages from 50mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in the rat and mouse. The rat study gave no indications of substance-related increases in tumour incidence. In the mouse study, increased incidence of liver cell adenoma was observed in the males (dose-dependent, non-significant increases from 15 mg/kg and an increase in lung tumours in the females of all dose groups (significant but nondose dependent increases).

6.1 List of excipients

Maize Starch

Green Cap/ Green Body”2” Hard Gelatin Capsule

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

10 Capsule packed in one ALU-PVC blister. 10 blisters packed in one carton

7. MARKETING AUTHORISATION HOLDER

ZAIN PHARMA LTD.

Plot No: 209/13741, Colchester Park,

Go-Down No.1, 2, 3, Off Mombasa Road,

Behind Nice And Lovely House,

P.O. Box: 100167-00101, Nairobi, Kenya

8 MARKETING AUTHORISATION NUMBER(S)

H2021/CTD7929/1728ER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2026 December 01

10 DATE OF REVISION OF THE TEXT

2026 December 01

