

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tramadol Kalceks 50 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg of tramadol hydrochloride.

For the full list of excipients, see *List of excipients*.

3. PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion).

Clear colourless liquid, free from visible particles.

Description after dilution: clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

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 tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed, Tramadol Kalceks should be administered as follows:

Adults and adolescents above the age of 12 years

Tramadol Kalceks is not approved for use in patients below 12 years old.

The usual dose is 50 or 100 mg 4-6 hourly.

Intravenous injections must be given slowly over 2-3 minutes.

For post-operative pain administer an initial bolus of 100 mg. During the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg - 100 mg 4-6 hourly up to a total daily dose of 400 mg.

Paediatric population

The safety and efficacy of Tramadol Kalceks has not been studied in the paediatric population. Therefore, use of Tramadol Kalceks is not recommended in patients under 12 years of age.

Geriatric patients

A dose adjustment is not usually necessary in elderly 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 insufficiency

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

The solution for injection is to be injected slowly or diluted in infusion solution and infused.

Routes of administration

Intravenous, intramuscular, subcutaneous.

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.

4.3 Contraindications

- Hypersensitivity to the active substance and/or to any of the excipients.
- Acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products.
- Patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section *Interaction with other medicinal products and other forms of interaction*).
- Patients with epilepsy not adequately controlled by treatment.
- For use in narcotic withdrawal treatment.
- Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

4.4 Special warnings and precautions for use

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians and Arabs. Data are not available for other ethnic groups.

Paediatric population

The safety and efficacy of Tramadol Kalceks has not been studied in the paediatric population. Therefore, use of Tramadol Kalceks is not recommended in patients under 12 years of age.

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.

Risks from concomitant use with benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Tramadol Kalceks with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Tramadol Kalceks is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See *Interaction with other medicinal products and other forms of interaction*).

Serotonin syndrome with concomitant use of serotonergic drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Tramadol Kalceks with serotonergic drugs (See *Interaction with other medicinal products and other forms of interaction*). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See *Interaction with other medicinal products and other forms of interaction*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Tramadol Kalceks if serotonin syndrome is suspected.

Respiratory depression

Administer Tramadol Kalceks cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of Tramadol Kalceks may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

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.

Adrenal insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a

different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual function/Reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See *Postmarketing experience*).

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.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section *Interaction with other medicinal products and other forms of interaction*), or if the recommended dosage is significantly exceeded (see *Overdose*) as the possibility of respiratory depression cannot be excluded in these situations.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when a dose of tramadol exceeds the recommended daily dose (400 mg). Tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section *Interaction with other medicinal products and other forms of interaction*). In patients with epilepsy or those susceptible to seizures, tramadol may only be used when absolutely necessary.

Tolerance, psychic and physical dependence may develop, especially after long-term use. Therefore, 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.

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

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

This medicinal product contains less than 1 mmol sodium (23 mg) per ml of solution, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ -receptors, and benzodiazepines interact at GABA_A sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see *Special warnings and precautions for use*).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Tramadol Kalceks if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants

(TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See *Special warnings and precautions for use*).

MAO inhibitors

Tramadol should not be used in combination with MAO inhibitors (see *Contraindications*).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions affecting 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.

Cimetidine

With concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Carbamazepine

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

CNS-active agents

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

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 products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Coumarin derivatives

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.

CYP3A4 inhibitors

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

Ondansetron

Pre- or postoperative application of the antiemetic 5-HT₃ antagonist ondansetron may increase the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. Tramadol Kalceks is not recommended for pregnant women.

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. Prolonged use during pregnancy may lead to neonatal withdrawal symptoms.

Lactation

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.

Fertility

Post marketing surveillance does not suggest 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 alcohol and other psychotropic substances.

4.8 Undesirable effects

The side effects mentioned below are listed according to MedDRA system organ classification. The frequencies are ranked according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are nausea and dizziness. These occur in more than 10% of patients.

Immune system disorders

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

Cardiac disorders

Uncommon: effect on cardiovascular regulation (palpitations, 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: effect on cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

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 lowering the seizure threshold (see sections *Special warnings and precautions for use* and *Interaction with other medicinal products and other forms of interaction*).

Not known: serotonin syndrome.

Metabolism and nutrition disorders

Rare: changes in appetite.

Not known: hypoglycaemia.

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).

Drug dependence may occur. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur. These include: 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).

Eye disorders

Rare: miosis, mydriasis, blurred vision.

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 *Interaction with other medicinal products and other forms of interaction*), respiratory depression may occur.

Worsening of asthma has been reported, though a causal relationship has not been established.

Not known: hiccups.

Gastrointestinal disorders

Very common: nausea.

Common: constipation, dry mouth, vomiting.

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Very rare: in a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis.

Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders

Rare: muscular weakness.

Renal and urinary disorders

Rare: micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions

Common: fatigue.

Postmarketing experience:

Serotonin syndrome (See *Special warnings and precautions for use*)

Adrenal insufficiency (See *Special warnings and precautions for use*)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

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 National Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

4.9 Overdose

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 should be taken. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In cases of convulsions 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 Kalceks with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, other opioids, ATC code: N02AX02

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ , δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition 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 to 1/6 that of morphine.

5.2 Pharmacokinetic properties

After intramuscular administration in humans, tramadol is absorbed rapidly and completely: the mean peak serum concentration (C_{max}) is reached after 45 minutes, and bioavailability is almost 100%. Tramadol has a high tissue affinity ($V_{d,\beta} = 203 \pm 40$ l). It has a plasma protein binding of about 20%.

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).

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. 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 patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), 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.

In humans, tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, 11 metabolites have been found in the urine. O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life, $t_{1/2,\beta}$ is 7.9 h (range 5.4-9.6 h) and is approximately that of tramadol.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The relationship between serum concentrations and the analgesic effect is dose-dependent, 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-desmethyltramadol after single-dose and multiple-dose oral administration in children aged 1 year to 16 years is 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 is not fully characterized. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Water for injections

6.2 Incompatibilities

Tramadol Kalceks should not be mixed with solutions for injection or infusion containing diclofenac, indomethacin, phenylbutazone, diazepam, midazolam, flunitrazepam and glyceryl trinitrate. This medicinal product must not be mixed with other medicinal products except those mentioned in section *Special precautions for disposal and other handling*.

6.3 Shelf life

4 years.

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6.4 Special precautions for storage

Unopened (before dilution): Do not store above 30°C.

Once ampoule has been opened: the product should be used immediately.

After dilution: To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

6.5 Nature and contents of container

1 ml of solution in type I hydrolytic class colourless borosilicate glass ampoule with break line or open point cut.

5 ampoules in a PVC liner. 2 liners (10 ampoules) in outer carton.

6.6 Special precautions for disposal and other handling

For single use only.

Tramadol is compatible with 0.9% sodium chloride or 5% glucose solution for infusion.

Calculation of injection volume

- 1) Calculate the total dose of tramadol hydrochloride (mg) required: bodyweight (kg) x dosage (mg/kg).
- 2) Calculate the volume (ml) of diluted solution to be injected: divide the total dose (mg) by an appropriate concentration of diluted solution (mg/ml; see table below).

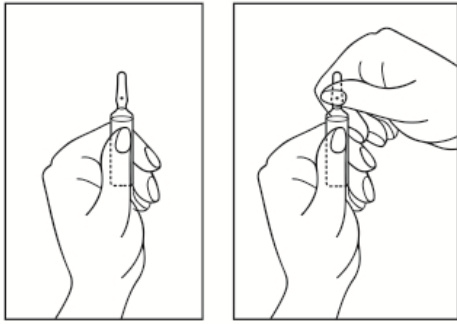
Table. Dilution of Tramadol Kalceks solution for injection/infusion

Concentration of diluted solution (mg tramadol hydrochloride/ml)	Tramadol Kalceks 50 mg/ml solution for injection/infusion (1 ml ampoule) + diluent added
25.0 mg/ml	1 ml + 1 ml
16.7 mg/ml	1 ml + 2 ml
12.5 mg/ml	1 ml + 3 ml
10.0 mg/ml	1 ml + 4 ml
8.3 mg/ml	1 ml + 5 ml
7.1 mg/ml	1 ml + 6 ml
6.3 mg/ml	1 ml + 7 ml
5.6 mg/ml	1 ml + 8 ml
5.0 mg/ml	1 ml + 9 ml

According to your calculation, dilute the contents of Tramadol Kalceks ampoule by adding a suitable diluent, mix and administer the calculated volume of diluted solution.

Instruction of ampoule opening:

- 1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
- 2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:

Eucogen Sdn Bhd

6A, Jalan Sungai Burung U

32/U, Bukit Rimau, 40460 Shah

Alam, Selangor, Malaysia

Manufacturer:

HBM Pharma s.r.o.

Sklabinska str., 30, Martin, 036 80

Slovakia

8. DATE OF REVISION OF THE TEXT

09/2023