SUMMARY OF PRODUCT CHARACTERISTICS

- Its use is contraindicated in children under 12 years of age.
- Its use is contraindicated for the treatment of pain after tonsil and/or adenoid surgery in children under the age of 18.
- It should not be used because of the higher risk of undesirable effects in children aged 12-18 years who are overweight, obese, with obstructive sleep apnea, with chronic lung problems.
- It should not be used during breastfeeding or alternatively, breastfeeding should be discontinued during tramadol treatment because of the risk of causing insomnia, restlessness, breastfeeding difficulties and respiratory problems in infants who are breastfed.

1. NAME OF THE MEDICINAL PRODUCT

TRAMOSEL 100mg/ 2 mL I.V./ I.M./ S.C. Ampoule Containing Solution for Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: 1 mL of solution contains 50 mg of tramadol hydrochloride. Each 2 mL ampoule contains 100 mg of tramadol hydrochloride.

Excipients:
Sodium Acetate Trihydrate 8.3 mg

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Ampoule Containing Solution for Injection.
Colorless, clear solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the treatment of moderate or severe pain.

4.2. Posology and method of administration

Posology /administration frequency and duration

Dose adjustment should be done according to the severity of pain and the individual response of the patient. In general, the lowest dose that will relieve pain should be chosen. The dose should be adjusted according to the severity of the pain and the sensitivity of the patient. Except in special clinical situations (tumor pain and severe postoperative pain), the daily dose of tramadol should not exceed 400 mg (4 ampoules).

In adults and adolescents over 12 years old:
The usual dose is 50 or 100 mg every 4-6 hours (see section 5.1).
Intravenous injections should be given slowly over 2-3 minutes.
For post-operative pain, administer an initial bolus of 100 mg. Additional doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg, including the initial bolus, over the 60 minutes following the first bolus. Subsequent doses should be 50 mg-100 mg every 4-6 hours up to a total daily dose of 400 mg.

Administration time:
In no case should TRAMOSEL be used longer than absolutely necessary. Depending on the origin and severity of the disease, if there is a need for long-term TRAMOSEL treatment, regular and careful evaluations should be made (if necessary, breaks should be made in the treatment) and it should be decided how long the treatment should be continued.

Route of administration:
IV administration is by slow injection or diluted infusion. The ampoules are also suitable for IM or SC administration.

Additional information on special populations:
Renal/ Hepatic impairment:
Elimination of tramadol is delayed in patients with renal and/or hepatic impairment. In these patients, the physician may consider extending the dose interval according to the patient's needs.

Pediatric population:
It is contraindicated in children under 12 years of age.

Geriatric population:
No dosage adjustment is required in patients up to 75 years of age without clinically evident hepatic or renal impairment. Elimination time may be prolonged in patients over 75 years of age. For this reason, dose intervals can be extended if necessary according to the needs of the patient.

4.3. Contraindications
TRAMOSEL is contraindicated in the following conditions.
- In patients with hypersensitivity to the active substance or any of its ingredients,
- In acute intoxications caused by alcohol, hypnotics, analgesics, opioids or drugs containing psychotropic substances,
- In patients taking MAO inhibitors or who have taken MAO inhibitors in the last 14 days (see section 4.5).
- It is contraindicated in epilepsy patients who cannot be controlled with treatment,
- For drug withdrawal treatment,
- its use is contraindicated in children under 12 years of age.

- Its use is contraindicated for the treatment of pain after tonsil and/or adenoid surgery in children under the age of 18.

4.4. Special warnings and precautions for use

- TRAMOSEL should be used with caution in opioid-dependent patients, in patients with head injuries, in shock, in cases of unknown cause that decrease the level of consciousness, in respiratory center or dysfunction, and in cases of increased intracranial pressure.
- It should be used with caution in patients sensitive to opioids.
- Concomitant use of TRAMOSEL and sedative medicinal products such as benzodiazepines or similar substances may result in sedation, respiratory depression, coma and death. Because of these risks, prescribing with these sedative drugs should be reserved for patients for whom alternative treatment options are not possible. If it is decided to prescribe TRAMOSEL with sedative drugs, the lowest effective dose of TRAMOSEL should be used and the duration of concomitant therapy should be as short as possible.
- Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this respect, it is recommended that patients and their caregivers be informed about these symptoms (See Section 4.5).
- If the patient being treated has respiratory depression or concomitant use of drugs that suppress the central nervous system (see section 4.5) or if the recommended dose is significantly exceeded (see section 4.9), treatment should be administered with caution as respiratory depression may occur in these situations.
- Convulsions have been reported in patients taking TRAMOSEL at recommended doses. The risk may be increased if the dose exceeds the maximum recommended daily dose (400 mg). In addition, TRAMOSEL increases the risk of seizures in patients taking other drugs that lower the seizure threshold (see section 4.5). In patients with epilepsy or those predisposed to seizures, TRAMOSEL should only be used if absolutely necessary.
- Sleep-related breathing disorders
  Opioids can cause sleep-related breathing disorders, including central sleep apnea and sleep-related hypoxemia. Opioid use increases the risk of central sleep apnea in a dose-dependent manner. Reducing the total opioid dose should be considered in patients presenting with central sleep apnea.

- Serotonin syndrome
  The potentially life-threatening condition serotonin syndrome has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see section 4.5, 4.8 and 4.9). If concomitant therapy with other serotonergic agents is clinically warranted, careful observation of the patient is recommended, particularly at the start of therapy and during dose increases.
  Symptoms of serotonin syndrome may include altered mental status, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

Serotonin syndrome is likely when one of the following is observed:
Spontaneous clonus
May be induced by agitation or sweating or ocular clonus
Tremor and hyperreflexia
Hypertonia and body temperature > 38 °C and inducible or ocular clonus

If serotonin syndrome is suspected, dose reduction or discontinuation of therapy should be considered, depending on the severity of symptoms. Discontinuation of serotonergic drugs usually provides a rapid recovery.

Drug dependence, tolerance and potential for abuse

Tolerance, psychological and physical dependence may develop, especially after long-term use.
When a patient no longer needs to be treated with tramadol, it may be advisable to gradually reduce the dose to avoid withdrawal symptoms.
It should not be used during breastfeeding or alternatively, breastfeeding should be discontinued during tramadol treatment because of the risk of causing insomnia, restlessness, breastfeeding difficulties and respiratory problems in infants who are breastfed.
For all patients, long-term use of this drug can lead to drug dependence (dependence), even at therapeutic doses. The risks are increased in people with a current or past substance abuse disorder (including alcohol abuse) or a mental health disorder (for example, major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid abuse.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medications, and past and current medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and may express the need to increase the dose to achieve the same level of pain control as they initially experienced. Patients can also supplement their treatment with additional pain relievers. These may be signs that the patient has developed a 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 the drugs given to them at the dose prescribed and not to give this drug to anyone else.
Patients should be closely monitored for signs of abuse, misuse or addiction. The clinical need for analgesic therapy should be reviewed regularly.

Drug withdrawal syndrome

Before initiating treatment with any opioid, patients should be interviewed to establish a withdrawal strategy for discontinuing tramadol therapy.
Drug withdrawal syndrome may occur due to abrupt discontinuation of treatment or reduction of dose. When a patient no longer needs therapy, it is recommended to gradually reduce the dose to minimize withdrawal symptoms. It may take weeks or months to reduce a high dose.

Opioid drug withdrawal syndrome is characterized by some or all of the following: Restlessness, tears, runny nose, yawning, sweating, tremors, myalgia, mydriasis and palpitations. Other symptoms may also develop, such as nervousness, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, loss of appetite, abdominal cramps, nausea, vomiting, diarrhea, increased blood pressure, increased respiratory rate or heart rate.
If women take this medicine during pregnancy, there is a risk that their newborn babies will experience neonatal abstinence syndrome.

- TRAMOSEL is not suitable for replacement therapy in opioid-dependent patients. Despite being an opioid agonist, TRAMOSEL cannot suppress morphine withdrawal symptoms.
- It should not be used because of the higher risk of undesirable effects in children aged 12-18 years who are overweight, obese, with obstructive sleep apnea, with chronic lung problems.
- Hyperalgesia
- If the patient on long-term opioid therapy has increasing pain, a diagnosis of hyperalgesia can be made.
- This may be qualitatively and anatomically different from pain associated with disease progression or severe pain from the development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse and less defined in quality than pre-existing pain. Symptoms of hyperalgesia may improve with reduction of the opioid dose.
- CYP2D6 Metabolism

  Tramadol is metabolized by the liver enzyme CYP2D6. If the patient has a deficiency or is completely deficient in this enzyme, an adequate analgesic effect may not be achieved. Estimates suggest that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metabolizer, there is a risk of developing opioid toxicity as a <side effect> even with commonly prescribed doses. General symptoms of opioid toxicity include confusion, sleepiness, shallow breathing, constricted pupils, nausea, vomiting, constipation, and loss of appetite. May include symptoms of severe respiratory depression. Estimates of prevalence in ultra-rapid metabolizers in different populations are summarized below:

Population	%Prevalence
African/Ethiopian	29%
African American	3.4% and 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Hellenic	6%
Hungarian	1.9%
Nordic	1% to 2%

- Post-operative use in children
  In the published literature, there are reports of rare, but life-threatening adverse events with tramadol given postoperatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnea. Extreme caution should be exercised when tramadol is administered to children for the relief of post-operative pain, and close monitoring should be exercised for concomitant symptoms of opioid toxicity, including respiratory depression.

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

- Adrenal insufficiency
  Opioid analgesics can sometimes cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme tiredness, decreased appetite and weight loss. TRAMOSEL contains less than 23 mg sodium per dose.

4.5. Interaction with other medicinal products and other forms of interaction

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

Concomitant use of TRAMOSEL with other CNS depressant medicinal products, including alcohol, may potentiate CNS effects (see section 4.8).

Concomitant use of opioids with sedative medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death due to the additive CNS depressant effect. The dose and duration of concomitant use of TRAMOSEL should be limited (see section 4.4).

Results of pharmacokinetic studies showed that administration of cimetidine (enzyme inhibitor) with or before TRAMOSEL is difficult to cause clinically relevant interactions. Concomitant or prior administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

Tramadol can cause convulsions and selective serotonin reuptake inhibitors (SSRIs), serotonin, norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics, and other seizure threshold lowering medicinal products (e.g. bupropion, mirtazapine, tetrahydrocannabinol) may cause convulsions. increases its potential.

The use of TRAMOSEL in combination with serotonergic drugs such as selective serotonin reuptake inhibitors (SSR) and serotonin norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonergic toxicity (See section 4.4 and 4.8).

Caution should be exercised when co-administering tramadol and coumarin derivatives (e.g. warfarin) has been reported in some patients, as major bleeding and ecchymoses with increased INR have been reported.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) and possibly the metabolism of its active O-demethylated metabolite. The clinical significance of such interactions has not been studied (see section 4.8).

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

4.6. Pregnancy and lactation

General advice

Pregnancy Category: C

Women of childbearing potential / contraception

Since the safety of tramadol in women has not been proven, TRAMOSEL should be used with caution in women who are not using contraception. Women using TRAMOSEL should use an appropriate method of contraception.

Pregnancy

In animal studies with tramadol, effects on organ development, bone growth and mortality rate in newborns have been observed at very high doses. Tramadol crosses the placenta. Little is known about the safety of tramadol in human pregnancy. Therefore, TRAMOSEL should not be used in pregnant women.

Regular use during pregnancy may cause drug dependence in the fetus, resulting in withdrawal symptoms in the newborn.

If a pregnant woman requires prolonged use of opioids, the patient should be informed of the risk of neonatal opioid withdrawal syndrome and appropriate therapy should be ensured.

Tramadol given before or during labor does not affect uterine contractions.

Administration during labor may suppress respiration in the newborn and an antidote should be available for the child.

Lactation period
It is not recommended to be administered to lactating women as tramadol may pass into breast milk and cause respiratory depression in the infant. Approximately 0.1% of the maternal dose of tramadol passes into breast milk. For a daily maternal oral dosage of up to 400 mg in the early postpartum period, this corresponds to an average amount of tramadol, corresponding to 3% of the maternal weight-adjusted dosage for breastfed infants. Therefore, tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during tramadol therapy. There is a risk that it may cause insomnia, restlessness, breastfeeding difficulties and respiratory problems in breastfed babies.

Reproductive ability / Fertility
Data from post-marketing observations indicate that tramadol has no effect on fertility. Animal studies have not shown an effect of tramadol on fertility.

4.7. Effects on ability to drive and use machines
TRAMOSEL can cause drowsiness and dizziness, thereby impairing the reaction of drivers or machine users. Do not drive and use machines while using TRAMOSEL. This situation occurs when used together with other psychotropic substances, especially alcohol.

4.8. Undesirable effects
Very common (≥1/10); common (≥1/100 to < 1 /10); uncommon (≥1/1000 and <1/100); rare (≥1/10.000 and <1/1000); very rare (< 1/10.000), unknown (cannot be estimated from the available data).

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

Immune system diseases
Rare : Allergic reactions (eg, dyspnea, bronchospasm, wheezing, angioneurotic edema) and anaphylaxis.

Metabolism and nutrition disorders
Rare: Appetite changes.
Unknown : Hypoglycemia

Psychiatric diseases
Rare : Hallucinations, confusional state, sleep disturbances, delirium, anxiety and nightmares. Psychic adverse reactions may occur following tramadol ingestion, varying in severity from person to person and depending on personality and duration of treatment. These

are changes in temperament (usually euphoria, sometimes dysphoria), changes in activity (usually suppression, sometimes increased), changes in cognitive and sensory capacities (e.g. decision-making behavior, perceptual disturbances).
Unknown : Drug addiction (See Section 4.4)

Nervous system diseases
Very Common : Dizziness (drowsiness)
Common : Headache, drowsiness
Rare :Speech disorders, epileptiform convulsions, paresthesia, tremor, involuntary muscle contractions, abnormal coordination, syncope.
Unknown : Serotonin syndrome
Convulsions have occurred mainly after high doses of tramadol or when used with medicinal products that may lower the seizure threshold (see sections 4.4 and 4.5).

Eye diseases
Rare : Blurred vision, miosis, mydriasis

Cardiac diseases
Uncommon : Cardiovascular regulation (palpitations, tachycardia). These adverse reactions may occur especially with intravenous administration and in patients with physical stress.
Rare : Bradycardia

Vascular diseases
Uncommon : Cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially with intravenous administration and in patients with physical stress.

Respiratory, pulmonary disorders and mediastinal diseases
Rare : Respiratory suppression, dyspnea
Respiratory depression may occur if the recommended doses are significantly exceeded, and other central depressant substances are taken concomitantly (see section 4.5).
Worsening of asthma has been reported, but a causal relationship has not been established.
Unknown : Hiccup

Gastrointestinal diseases
Very Common : Nausea
Common : Vomiting, constipation, dry mouth
Uncommon : Gagging; gastrointestinal discomfort (stomach pressure feeling, bloating), diarrhea

Hepato-bilier diseases
In a few isolated cases, increases in liver enzyme values have been reported in temporal association with tramadol therapy.

Skin and subcutaneous tissue diseases
Common : Hyperhidrosis
Uncommon : Skin reactions (eg itching, rash, urticaria)

Musculoskeletal, connective tissue and bone disorders
Rare : Motor weakness

Kidney and urinary tract diseases
Rare : Voiding disorders (dysuria and urinary retention)

General disorders and administration site conditions
Common : Tiredness
Uncommon : Drug withdrawal syndrome

Researches
Rare : Increase in blood pressure.

Withdrawal reaction symptoms similar to those that occur during opioid withdrawal may occur. These symptoms are: agitation, anxiety, nervousness, sleep disturbances, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms very rare upon discontinuation of tramadol: panic attacks, severe anxiety, hallucinations, paresthesias, tinnitus and unusual central nervous system symptoms (e.g. confusion, delusions, depersonalization, derealization, paranoia).

Reporting of the side effects:
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment
Patients should be informed of the signs and symptoms of overdose and should make family and friends aware of these signs and seek immediate medical attention if they occur.

Symptoms
In principle, the symptoms of tramadol poisoning are expected to be similar to the effects of other centrally acting analgesics (opioids). These are especially miosis, vomiting, cardiovascular collapse, disturbances of consciousness up to coma, convulsions and respiratory depression up to respiratory arrest.

Serotonin syndrome has also been reported.
Treatment
General emergency response principles apply. The airway is kept open (aspiration), and breathing and circulation are maintained according to the symptoms. The antidote for respiratory depression is naloxone. In animal experiments, naloxone had no effect on convulsions. In these cases, intravenous diazepam should be given.

In case of oral intoxication, gastric decontamination by administration of activated charcoal and gastric lavage should be done within 2 hours of ingestion of tramadol. It can also be applied later in case of high doses or slow-release formulation poisoning. Gastrointestinal decontamination at a later time point may be beneficial, exceptionally in case of poisoning in large quantities or with extended-release formulations.

Tramadol is minimally eliminated from serum by hemodialysis or hemofiltration. Therefore, treatment of acute poisoning with TRAMOSEL alone with hemodialysis or hemofiltration 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 pure non-selective agonist on μ, δ and κ opioid receptors; It has higher affinity for μ receptors. Other mechanisms contributing to its analgesic effect are inhibition of neuronal noradrenaline reuptake and increased serotonin release.

Tramadol also has an antitussive effect. Unlike morphine, analgesic doses of tramadol do not produce a respiratory depressant effect over a wide range. Gastrointestinal motility is also less affected.

Effects on the cardiovascular system tend to be mild. The potency of tramadol is reported to be between 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Pediatric population:
The effects of enteral and parenteral administration of tramadol have been studied in clinical studies involving more than 2000 pediatric patients from neonate to 17 years of age. The analgesia indications examined in these studies; postoperative pain (especially abdominal), post-extraction pain, fracture, burn and trauma, and other painful conditions requiring 7-day analgesic treatment.

At single doses of 2 mg/kg or multiple doses of up to 8 mg/kg/day (up to 400 mg/day), the

efficacy of tramadol was greater than placebo and greater than or equal to paracetamol, nalbuphine, pethidine, or low-dose morphine. The safety profile of tramadol was similar in adults and pediatric patients over 1 year of age.

5.2. Pharmacokinetic Properties

Absorption:

Tramadol is rapidly and completely absorbed after intramuscular administration; The mean peak serum concentration (C_{max}) is reached after 45 minutes and the bioavailability is approximately 100%. More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70% regardless of concomitant meals. The possible reason for this difference between available tramadol and non-metabolized tramadol is the first-pass effect. The first pass effect after oral administration is a maximum of 30%.

The maximum plasma concentration of tramadol in liquid form is reached 1.2 hours after oral administration, with C_{max}=309±90 ng/mL. The maximum plasma concentration of the same dose of tramadol after administration in solid form was reached 2 hours later and C_{max}=280±49 ng/mL.

Distribution:

Tramadol has a high tissue affinity ($V_{d,ß}$ = 203±40 L). It is approximately 20% bound to plasma proteins.

Tramadol crosses the blood-brain barrier and the placental barrier. Milk contains very small amounts of the active substance and the O-desmethyl derivative (0.1% and 0.02% of the administered dose, respectively).

Biotransformation:

In humans, tramadol is metabolized primarily by N- and O-demethylation and conjugation of O-demethylated products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are significant interindividual quantitative differences among other metabolites. So far, 11 metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is 2-4 times more potent than the parent compound. The half-life is $t_{1/2.ß}$ (6 healthy volunteers) 7.9 hours (range 5.4 - 9.6 hours) and approximately that of tramadol.

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

Elimination:

The elimination half-life is approximately 6 hours, regardless of the $t_{1/2,ß}$ route of administration. It can be prolonged approximately 1.4 times in patients over 75 years of age.

Tramadol and its metabolites are almost completely excreted by the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. The half-life may be slightly prolonged in hepatic and renal dysfunction. In patients with liver cirrhosis, the elimination half-life has been shown to be 13.3 ± 4.9 hours (tramadol) and 18.5 ± 9.4 hours (O-desmethyltramadol), 22.3 hours and 36 hours, respectively, in one extreme case. In patients with renal impairment (creatinine clearance < 5 mL/min), the values were 11 ± 3.2 hours and 16.9 ± 3 hours, 19.5 hours and 43.2 hours in one extreme case, respectively.

Tramadol has a linear pharmacokinetic profile over the therapeutic dose range.

The relationship between serum concentrations and analgesic effect is dose dependent but varies markedly in some cases. Usually a serum concentration of 100-300 mg/mL is effective.

Pediatric population:
Single or multiple oral dose pharmacokinetic data for tramadol and O-desmethyltramadol in patients 1-16 years of age were generally similar to adults when dosed according to body weight, but with greater interindividual variability in children 8 years and younger.

Pharmacokinetic data of tramadol and O-desmethyltramadol in children under 1 year of age have been investigated but not fully defined. Information from studies including this age group shows that the rate of O-desmethyltramadol formation via CYP2D6 is constantly increased in infants, and the CYP2D6 activity level of adults is reached at 1 year of age. In addition, the immature glucuronidation system and renal function in children under 1 year of age may result in slow elimination and accumulation of O-desmethyltramadol.

5.3. Pre-clinical safety data

When tramadol was administered orally and parenterally for 6-26 weeks in rats and dogs and repeated orally for 12 months in dogs, hematological, clinical, chemical and histological examinations showed no evidence of any substance-related changes. Central nervous system symptoms occurred only after high doses significantly above the therapeutic range: Decreased restlessness, salivation, convulsions and weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg, respectively, and dogs tolerated 20 mg/kg rectal doses without any reaction.

Tramadol doses above 50 mg/kg/day in rats caused toxic effects in the mother and increased neonatal mortality. Developmental delay in the form of ossification disorders, delay in vaginal and eye opening occurred in puppies. Male fertility was not affected. After higher doses (more than 50 mg/kg/day) females had a lower pregnancy rate. Rabbits had maternal toxic effects and offspring skeletal abnormalities at doses above 125 mg/kg.

There was evidence of mutagenic effect in some in-vitro test systems. In-vivo studies did not show such effects. Based on the information available so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been performed in rats and mice. Studies in rats showed no evidence of any substance-related increase in tumor incidence. In studies in mice, there was an increase in the incidence of liver cell adenomas in males (no significant dose-dependent increase at doses above 15 mg/kg) and an increase (significant, but not dose-dependent) of pulmonary tumors in females in all dose groups.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients:

Sodium acetate trihydrate
Water for injection

6.2. Incompatibilities

Incompatible with diclofenac, indomethacin, phenylbutazone, diazepam, flunitrazepam, midazolam, glyceryltrinitrate injectable solutions.

6.3. Shelf Life

36 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Packaging containing 5 ampoules of 2 mL.

6.6. Destruction of the residual materials human medicinal product and other special precautions

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

253/42

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First authorization date: 20.09.2013
Renewal date: 01.11.2019

10. DATE OF REVISION OF THE TEXT