PATIENT INFORMATION LEAFLET

- **DO NOT USE TRAMOSEL in children under 12 years of age.**
- **DO NOT USE TRAMOSEL in children under 18 years of age for the treatment of pain after tonsil (tonsil) and / or adenoid (adenoid) surgeries.**
- **DO NOT USE TRAMOSEL in children aged 12-18 years who are overweight, obese, obstructive sleep apnea (frequent breathing during sleep) or have chronic lung problems..**
- **If you are a breastfeeding mother, DO NOT USE TRAMOSEL or stop breastfeeding as it may cause insomnia, restlessness, breastfeeding difficulties and breathing problems in your baby.**

TRAMOSEL 100 mg / 2 mL I.V./I.M./S.C. ampoule containing solution for injection

For intravenous, intramuscular or subcutaneous administration.
Sterile

- ***Active Ingredient:*** Each ampoule(2 mL) contains 100 mg tramadol hydrochloride
- ***Excipients:*** Sodium acetate trihydrate, water for injection.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use **high or low doses** other than the recommended dosage.*

What is in this leaflet:

1. What TRAMOSEL is and what it is used for?

TRAMOSEL contains 5 ampoules of 2 mL in each box.

Tramadol, the active ingredient of TRAMOSEL, is a pain reliever that affects the central nervous system. It relieves pain by acting on special nerve cells in the spinal cord and brain.

TRAMOSEL is used in the treatment of moderate or severe pain.

2.What you need to know before you use TRAMOSEL

DO NOT USE TRAMOSEL in the following situations

- Children under 12 years old;
- For the treatment of pain after tonsil and / or adenoid surgeries in children under the age of 18;
- If you are allergic (hypersensitive) to tramadol or any of the other ingredients in TRAMOSEL;
- In case of acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic drugs (drugs that affect mood and emotions);
- If you are taking MAO inhibitors (some medicines used in the treatment of depression) or taken within 14 days of TRAMOSEL treatment (see "Use with other drugs");
- If you have epilepsy (epileptic) and your seizures are not adequately controlled by treatment;
- • Instead of narcotic drugs in narcotic drug withdrawal.

USE TRAMOSEL CAREFULLY;

If;

- In children aged 12-18 years with overweight, obese, obstructive sleep apnea or chronic lung problems;
- You think you are dependent on other pain relievers (opioids);
- You are unconscious (feeling faint);
- You are in shock (cold sweating may be a sign of this);
- You have increased intracranial pressure (possibly after a head injury or brain disease);

- You have difficulty breathing;
- You are prone to epilepsy or seizures, as the risk of seizures may increase;
- You have liver or kidney disease.

In these cases, consult your doctor before taking this medicine.
Epileptic seizures have been reported in patients taking tramadol at the recommended dose level. The Risk may increase when tramadol doses exceed the recommended daily upper limit (400 mg).
Note that TRAMOSEL can lead to physical and psychological dependence.
When TRAMOSEL is used for a long time, its effect may be reduced, so higher doses may be required (development of tolerance). In patients with a predisposition to drug abuse or addiction, treatment with TRAMOSEL should be carried out under strict medical supervision and only for short periods of time.
Tramadol is activated by liver enzymes in the body. If you have a deficiency of these enzymes or if this enzyme is completely absent, a sufficient pain relief effect may not be obtained.
Conversely, if these enzymes work very fast genetically in you (3.6 to 6.5% of these enzymes work fast in the Caucasian race), there is a risk of opioid poisoning even at the usual doses recommended for you. Common symptoms of opioid poisoning include confusion, drowsiness, shallow breathing, narrowed pupils, nausea, vomiting, constipation, and anorexia. In addition, a severe suppression of our left can be seen.
Psychological and physical dependence can develop with ineffectiveness to this drug, especially after long-term use.
It is recommended to gradually reduce the dose when you no longer need treatment to prevent withdrawal symptoms.
Because of the risk of insomnia, restlessness, difficulty in breastfeeding and respiratory problems in breastfed babies, it should not be used during breastfeeding or alternatively breastfeeding should be discontinued during tramadol therapy.

If these warnings are valid for you, even at any time in the past, please consult your doctor.

Use of TRAMOSEL with food and drink
Do not drink alcohol during TRAMOSEL therapy, as the effect may be exacerbated. It has no interaction with food and drink.

Pregnancy

Consult your doctor or pharmacist before using this medication.

There is very little information about the safety of tramadol during pregnancy in humans. For this reason, do not use TRAMOSEL if you are pregnant.

Repeated use during pregnancy can lead to physical dependence or withdrawal symptoms in the newborn.

If you notice that you are pregnant during treatment, consult your doctor or pharmacist.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

If you are a breastfeeding mother, do not use TRAMOSEL or stop breastfeeding as it may cause insomnia, restlessness, breastfeeding difficulties and respiratory problems in your baby.

Driving and using machines

TRAMOSEL may cause drowsiness, drowsiness, dizziness and blurred vision and thus impair your reactions. If you think your reactions are affected, do not drive cars or other vehicles, do not use electrical devices or operate machinery.

Important information about some of the excipients in TRAMOSEL

TRAMOSEL contains less than 23 mg sodium per dose; no sodium-related side effects are expected at this dose.

Using other medicines

TRAMOSEL should not be used in combination with MAO inhibitors (some drugs used in the treatment of depression).

If you use medicines containing the following substances, the pain relieving effect of TRAMOSEL may decrease and the duration of action may be shortened:

- Carbamazepine (for epileptic seizures);
- Pentazocine, nalbuphine, or buprenorphine (pain relievers);
- Ondansetron (anti-nausea).

Your doctor will tell you whether to take TRAMOSEL and what dose to take.

The risk of side effects increases in the following cases:

- While taking TRAMOSEL, you are taking other painkillers such as trancilizers, sleeping

pills, morphine and codeine (which is also a cough suppressant), and alcohol. You may feel lethargic or fainting. Tell your doctor if this happens.

- If you are taking medicines that can cause convulsions (seizures) such as some antidepressants. At the same time, if you are using TRAMOSEL, your risk of having a seizure may increase. Your doctor will tell you whether TRAMOSEL is suitable for you.
- If you are using some antidepressants, TRAMOSEL may interact with these drugs and involuntary, uncontrolled sudden contractions in the muscles, including the muscles that control eye movements, agitation (restlessness), excessive sweating, tremors, increased reflexes, increased muscle tension, body temperature above 38° C symptoms may occur.
- If you are using coumarin group anticoagulants (medicines used to thin the blood), eg warfarin, together with TRAMOSEL. The effects of these drugs on blood clotting may be affected and bleeding may occur.

If you are currently using any prescription or non-prescription medicine or have used it recently, please inform your doctor or pharmacist about them.

3. How to use TRAMOSEL

Instructions for use and dose/administration frequency:

Take TRAMOSEL exactly as your doctor told you. If you are not sure, talk to your doctor or pharmacist again.

The dosage should be adjusted according to the severity of your pain and your sensitivity to pain. In general, the lowest dose that will relieve pain should be chosen.

Unless otherwise prescribed by your doctor, the usual dose is:

Adults and adolescents over 12 years of age: It is recommended that the dose not exceed 2 mg / kg administered at one time. Depending on the severity of the pain, the effect lasts between 4-6 hours. 400 mg of tramadol (4 ampoules) per day should not be exceeded.

You should not use TRAMOSEL for longer than necessary. If you need longer-term treatment, your doctor will check whether you should continue to use TRAMOSEL at regular short intervals (by discontinuing treatment when necessary) and at what dose.

Method of administration

Intravenous administration is by slow injection or infusion. The ampoules are also suitable for intramuscular or subcutaneous administration.

Various age groups:

Use in children:

It is not used in children under 12 years of age.

For doctors and medical staff; Information on the application of the ampoule to children is given at the end of this patient information leaflet.

Use in elderly:

No dose adjustment is necessary in patients up to the age of 75 years without clinically significant hepatic or renal impairment. Excretion of tramadol from the body may be delayed in patients over 75 years of age. If you have such a condition, your doctor may extend the dose interval.

Special cases of use:

Renal/ Hepatic failure: Patients with severe hepatic and / or renal impairment should not take TRAMOSEL. If you have mild or moderate impairment, your doctor may recommend that you extend the dose interval.

If you have an impression that the effect of TRAMOSEL is too strong or too weak, talk to your doctor or pharmacist.

If you use more TRAMOSEL than you should

If you have accidentally taken an additional dose, this usually does not have negative effects. You should take the next dose as directed.

After taking very high doses, a pinhead-sized pupil, vomiting, drop in blood pressure, rapid heartbeat, disturbances in consciousness up to coma (deep unconsciousness), epileptic seizures, breathing difficulties to varying degrees may occur. In these cases, the doctor should be contacted immediately.

Talk to a physician or pharmacist if you have used more TRAMOSEL than you should use.

If you forget to use TRAMOSEL

If you forget to administer TRAMOSEL, the pain will probably return. Do not take a double dose to replace forgotten doses, just continue taking the drug as before

Do not take double doses to make up for forgotten doses.

Effects that may occur when treatment with TRAMOSEL is terminated

If you stop or take a break from TRAMOSEL treatment, the pain will likely return. If you want to stop treatment because of side effects, please talk to your doctor.

When TRAMOSEL treatment is discontinued, there will generally be no aftereffects. However, in some rare cases, people who have been using TRAMOSEL for a while may feel discomfort if they stop taking the medication suddenly. They may feel constant restlessness, anxiety, irritability, and tremors. They can be hyperactive, have trouble sleeping, and stomach or bowel

disorders. In very rare cases, unusual perceptions such as panic attacks, hallucinations, itching, tingling and numbness, and tinnitus may develop. If any of these complaints occur after stopping TRAMOSEL, please consult your doctor.

4. Possible side effects

As with all medicines, there may be side effects in people who are sensitive to the ingredients of TRAMOSEL.

If you notice any of the following, stop using TRAMOSEL and inform your doctor IMMEDIATELY, or apply to the emergency service of the nearest hospital:

- Swelling of the hands, feet, ankles, face, lips or swelling of the mouth or throat that makes it difficult to swallow or breathe.
- Rash, itching
- Fainting

These are all very serious side effects.
If you have one of these, it means you have a serious allergy to TRAMOSEL. You may need urgent medical attention or hospitalization.

Very common: It can be seen in at least one of 10 patients.

Common: It can be seen less than one in 10 patients, but more than one in 100 patients.

Uncommon: It can be seen less than one in 100 patients, but more than one in 1,000 patients.

Rare: It can be seen less than one in 1,000 patients, but more than one in 10,000 patients.

Very rare: It can be seen may be seen less than one in 10,000 patients.

Unknown frequency: Cannot be estimated from the available data.

Very common:

- Dizziness
- Nausea

Common:

- Headache, drowsiness
- Vomiting, constipation, dry mouth
- Excessive sweating
- Tiredness

Uncommon:

- Palpitations, postural hypotension (drop in blood pressure seen with sudden standing up or changing position)

- Gagging, feeling of pressure in the stomach, bloating, diarrhea
- Itching, rash, hives

Rare:

- Speech disorders
- Loss of feeling and strength, weakness in muscles
- Tremors, convulsions involuntary muscle contractions, abnormal coordination
- Fainting
- Excessive enlargement or shrinkage of the pupils, blurred vision
- Slow heart rate
- Respiratory suppression, difficulty breathing
- Urination disorders
- Changes in appetite
- Allergic responses (eg shortness of breath, wheezing, edema)
- Increase in blood pressure
- Hallucinations, confusion, sleep disturbances, irritability, nightmares, mood changes, addiction, as well as withdrawal reaction symptoms such as agitation, irritability, hyperkinesia, tremor.

Side effects that can be seen very rarely with the discontinuation of TRAMOSEL:

- Panic attacks, severe restlessness, hallucinations
- Tingling, numbness, and prickling sensations
- Tinnitus
- Stagger
- Delusion, detachment from reality, paranoia

If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

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.

5.How to store TRAMOSEL

Keep TRAMOSEL out of the reach and sight of children and within its packaging.

Store at room temperature below 25 ° C.

Use in compliance with the expiry date.

Do not use TRAMOSEL after the expiry date which is stated on the packaging.

Do not throw away expired or unused medicines! Give it to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Authorization Holder:

HAVER FARMA İlaç A.Ş.

Akbaba Mah. Maraş Cad. No:52/2/1

Beykoz / İSTANBUL

Manufacturer:

Osel İlaç Sanayi ve Tic A.Ş.

Akbaba Mah. Maraş Cad. No: 52 34820

Beykoz / İSTANBUL

This patient information leaflet approved in ../../....

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

TRAMOSEL 100 mg / 2 mL I.V./I.M./S.C. ampoule containing solution for injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each ampoule contains 100 mg tramadol hydrochloride.

Excipients:
Sodium acetate.$3H_2O$ 8.3 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Ampoule.
Colorless, clear solution

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

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

4.2. Posology and method of administration

Dose adjustment should be made according to the severity of the pain and the individual response given by the patient. In general, the lowest dose should be chosen to relieve the pain. The dose should be adjusted according to the severity of the pain and the sensitivity of the patient. The daily dose of tramadol should not exceed 400 mg (4 ampoules), except in special clinical cases.

Adults and adolescents over 12 years old: It can be administered at a dose of 50-100 mg tramadol every 4-6 hours.

In treatment with TRAMOSEL, the duration of treatment should be kept short and intermittent application should be performed in possible indications in order to prevent the occurrence of drug addiction and withdrawal symptoms. In long-term treatment with TRAMOSEL, the possibility of addiction should not be completely ruled out. For this reason, the doctor should decide on the duration of the treatment and, if necessary, temporarily stopping the drug.

Method of Administration:
IV administration is done by slow injection or infusion. The ampoules are also suitable for IM or SC administration. See 6.6 for instructions on dilution before administration.

Additional information on special populations

Renal/Hepatic Impairment:
In patients with renal and/or hepatic insufficiency, the elimination of tramadol is delayed. Patients with severe hepatic and/or renal failure should not take TRAMOSEL. In patients with mild or moderate renal and/or hepatic insufficiency, the physician may consider extending the dose range.

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

Geriatric population
No dose adjustment is necessary in patients up to the age of 75 years without clinically significant hepatic or renal impairment. The elimination time may be prolonged in patients over 75 years of age. Therefore, dosage intervals can be extended if necessary.

4.3. Contraindications

TRAMOSEL is contraindicated in the following situations.

- Hypersensitivity to tramadol or any of its ingredients,
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or drugs containing psychotropic substances,
- In patients who have received MAO inhibitors or have received MAO inhibitors in the last 14 days.
- In patients with epilepsy that cannot be controlled with treatment,
- For drug withdrawal treatment
- It is contraindicated in children under 12 years of age.
- In children under the age of 18; it is contraindicated for the treatment of pain after tonsil and / or adenoid surgery.

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 uncertain reason reducing 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.
- If the treated patient has respiratory depression, or if drugs that suppress the central nervous system are used at the same time, or if the recommended dose is significantly exceeded, respiratory depression may occur in these cases.
- Convulsions have been reported in patients taking tramadol hydrochloride at recommended doses. The risk may increase if the dose exceeds the recommended daily maximum dose (400 mg). In addition, TRAMOSEL increases the risk of seizures in patients taking other drugs that lower the seizure threshold. In patients with epilepsy or in patients with a predisposition to seizures, TRAMOSEL should only be used if necessary.
- The addictive potential of TRAMOSEL is low. Long-term use can develop tolerance, physical and psychological dependence. In patients prone to drug abuse or addiction, TRAMOSEL therapy should be administered for short periods of time and under serious medical supervision.
- TRAMOSEL is not suitable for replacement therapy in opioid-dependent patients. Although it is an opioid agonist, TRAMOSEL cannot suppress morphine withdrawal symptoms.
- In children aged 12-18; those who are overweight, those who are obese, those who have obstructive sleep apnea, children with chronic lung problems; it should not be used because the risk of undesirable effects is higher.
- CYP2D6 Metabolism

Tramadol is metabolized by the CYP2D6 liver enzyme. If the patient has a deficiency or if this enzyme is completely missing, a sufficient analgesic effect may not be obtained. Estimates suggest that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-fast metabolizer, there is a risk of developing opioid toxicity as a <side effect> even with commonly prescribed doses. Common symptoms of opioid toxicity include confusion, drowsiness, superficial breathing, narrowed pupils, nausea, vomiting, constipation, and anorexia. May include severe respiratory depression symptoms. The prevalence estimates in ultra-fast metabolizers in different populations are summarized below:

Population	Prevelance%
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%
Nordic	1% to 2%

- Tolerance, psychological and physical dependence may develop, especially after prolonged use.
- When a patient no longer needs to be treated with tramadol, it may be advisable to reduce the dose gradually to avoid withdrawal symptoms.
- Because of the risk of insomnia, restlessness, difficulty in breastfeeding and respiratory problems in breastfed babies, it should not be used during breastfeeding or alternatively breastfeeding should be discontinued during tramadol therapy.

This medicinal product contains less than 1 mmol (23 mg) sodium per ampoule. No adverse effects due to sodium are expected at this dose.

4.5. Interactions with other medical products and other forms of interaction

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

Concomitant use of TRAMOSEL with other central nervous system depressing medicinal products, including alcohol, may potentiate the effects of CNS (see section 4.8).

Results of pharmacokinetic studies have shown that the administration of cimetidine (mixed-function oxidase enzyme inhibitor) with or before tramadol hydrochloride 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.

The combination of mixed agonists / antagonists (e.g. buprenorphine, nalbufin, pentazosin) and tramadol is not recommended as it can theoretically reduce the analgesic effect of a pure agonist such as tramadol.

Tramadol can cause convulsions and can be used with selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, antipsychotics and other medicinal products that lower the seizure threshold (eg. Bupropion, mirtazapine, tetrahydrocannabinol) increases the potential to cause convulsions.

Combination of TRAMOSEL with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRs) serotonin norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonergic toxicity. The possibility of serotonin syndrome should be considered in the presence of either of the following:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Inducible or ocular clonus accompanied by hypertonia and body temperature above 38°C.

Discontinuation of serotenergic drugs usually provides a rapid recovery. Treatment depends on the type and severity of symptoms.

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

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 the active O-dimethylated 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 with childbearing potential/Contraception

Studies on experimental animals are insufficient in terms of effects on pregnancy and/or embryonal/fetal development and/or birth and/or postpartum development. In experimental animals, high doses have been shown to be effective on organ development, ossification, and neonatal mortality. The potential risk to humans is unknown. Tramadol given before or during labor does not affect uterine contractions, but should not be used during labor. It may cause changes in respiratory rate that are not clinically significant in newborns. Chronic use during pregnancy can lead to neonatal withdrawal symptoms.
TRAMOSEL should not be used during pregnancy unless necessary.

Pregnancy

Tramadol crosses the placenta. There is very little information about the safety of tramadol during pregnancy in humans. This is why TRAMOSEL should not be used in pregnant women.

Lactation

Approximately 0.1% of the maternal dose of tramadol passes into breast milk. In the early post-partum period, for a daily maternal oral dosage of up to 400 mg, this corresponds to an average amount of tramadol corresponding to 3% of the dosage adjusted by the maternal weight of breastfed infants. Therefore, tramadol should not be used during breastfeeding or alternatively breastfeeding should be discontinued during tramadol therapy. There is a risk of insomnia, restlessness, difficulty in

breastfeeding and respiratory problems in babies who are breastfed.

The reproductive capability/Fertility

Data from post-marketing observations show that tramadol has no effect on reproductive ability. Animal studies have not shown the effect of tramadol on fertility.

4.7. Effects on ability to drive and use machines

TRAMOSEL can cause drowsiness and dizziness and thus disrupt the reactions of drivers or machine users. Do not drive and use machines when using TRAMOSEL. This condition occurs in combination with other psychotropic substances, especially alcohol.

4.8. Undesirable effects

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) and unknown (estimation based on the existing data is impossible).

The most common reported adverse reactions with the use of tramadol hydrochloride are nausea and dizziness, both of which occur in more than 10% of patients.

Psychiatric disorders

Rare : Hallucinations, confusional state, sleep disturbances, delirium, anxiety and nightmares. Psychic adverse reactions may occur following taking TRAMOSEL, depending on the severity and characteristics of the individual and duration of treatment. These are mood changes (usually euphoria, sometimes dysphoria), changes in activity (usually suppression, sometimes increased), changes in cognitive and sensory capacity (eg decision-making behavior, perception disorders). Drug addiction may occur. Symptoms of withdrawal reactions similar to those that occur during opiate withdrawal may occur. These symptoms are: agitation, anxiety, irritability, insomnia, hyperkinesia, thermore and gastrointestinal symptoms.

Very rare : Panic attacks, severe anxiety, hallucinations, paresthesias, tinnitus and unusual central nervous system symptoms (eg confusion, delusions, depersonalization, rupture from reality, paranoia) may be observed with the withdrawal of tramadol.

Nervous system disorders

Very common : Dizziness

Common : Headache, drowsiness (somnolence)

Rare : Changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform

convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.
Respiratory depression can occur if the recommended doses are significantly exceeded and other central depressants are taken together (see Section 4.5).
Epileptiform convulsions occurred mainly after high doses of tramadol or when used in combination with medicinal products that can lower the seizure threshold (see sections 4.4 and 4.5).

Eye disorders
Rare : Blurred vision, miosis, mydriasis.

Cardiovascular disorders
Uncommon : Cardiovascular regulation (palpitations, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur particularly on intravenous administration and in physically stressed patients.

Rare : Bradycardia, increase in blood pressure

Respiratory, thoracic and mediastinal disorders
Rare: Respiratory suppression, dyspnea

If the recommended doses are significantly exceeded and other central depressant substances are taken together (see section 4.5), respiratory depression may occur.

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

Gastrointestinal system disorders:
Very common : Nausea

Common : Vomiting, constipation, dry mouth

Uncommon : Gagging; gastrointestinal irritation (feeling of pressure in the stomach, bloating), diarrhea

Hepato-biliary disorders:
In a few isolated cases, increases in liver enzyme values have been reported in temporal connection with tramadol therapy.

Skin and subcutaneous tissue disorders
Common : Sweating

Uncommon : Skin reactions (eg pruritus, rash, urticaria).

Musculoskeletal disorders

Rare: Motor weakness

Renal and urinary tract diseases

Rare: Voiding disturbances (difficulty urinating, dysuria and urinary retention)

General disorders and administration site conditions

Common : Fatigue

Rare : Allergic reactions (eg dyspnoea, bronchospasm, wheezing, angioneurotic edema) and anaphylaxis; Withdrawal reaction symptoms similar to those occurring during opiate withdrawal may occur; these symptoms are: Agitation, anxiety, irritability, insomnia, hyperkinesia, tremor, and gastrointestinal symptoms. Other symptoms that very rarely occur with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paresthesias, tinnitus and unusual central nervous system symptoms (e.g. confusion, delusions, personalization, rupture, paranoia).

Immune system disorders

Rare : Allergic reactions (eg dyspnoea, bronchospasm, wheezing, angioneurotic edema) and anaphylaxis.

Metabolism and nutrition disorders

Rare: Changes in appetite

Reporting of suspected adverse reactions

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

Symptoms
In principle, the symptoms of poisoning with tramadol are expected to resemble the effects of other central-acting analgesics (opioids). These are especially myosis, vomiting, cardiovascular collapse, disorders of consciousness ranging from coma, convulsions and respiratory depression up to cessation of breathing.

Treatment
General emergency response principles are applied. The airway is kept open (aspiration!), respiratory and circulation are maintained according to the symptoms. The stomach is emptied by vomiting (in unconscious patients) or gastric washing. The antidote for respiratory depression is naloxone. In animal experiments, naloxone has no effect on convulsions. In these cases, diazepam should be given intravenously.

Tramadol is minimally eliminated from the serum by hemodialysis or hemofiltration. Therefore, treatment of acute poisoning with TRAMOSEL by hemodialysis or hemofiltration alone is not suitable for detoxification.

Gastric decontamination with activated charcoal and gastric lavage should be done within 2 hours after ingestion of tramadol. In case of high doses or slow-release formulation poisoning, it may be administered later.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics / Other opioids
ATC Code: N02AX02

Tramadol is an opioid analgesic that acts centrally. It is a pure agonist that is not selective 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.

Tramadol also has an antitussive effect. Unlike morphine, analgesic doses of tramadol do not produce respiratory depressant effects 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) and 1/6 (one-sixth) of that of morphine.

5.2. Pharmacokinetic properties

Absorption:
Tramadol is rapidly and completely absorbed after intramuscular administration. The mean peak serum concentration (Cmax) is reached after 45 minutes and the bioavailability is approximately 100%.
More than 90% of tramadol is absorbed after oral administration. The absorption half-Life is 0.38±0.18 hours.
Compared to areas under serum tramadol concentration curves after Oral and iv administration, bioavailability for tramadol capsules was shown to be 68±13%.
Compared to other opioid analgesics, the absolute bioavailability of tramadol capsules is quite high. Peak plasma concentration is reached after 2 hours after administration of capsules.
After administration of 100 mg tramadol tablets, the peak plasma concentration of Cmax =141±40 ng/mL is reached after 4.9 hours. After administration of 200 mg tablets, peak plasma concentration with Cmax=260±62 ng/mL is reached after 4.8 hours. There is no significant difference between the pharmacokinetics of the tablet and oral drip and the pharmacokinetics of the capsule in terms of the degree of bioavailability measured as AUC. There is a 10% difference between the Cmax values of the oral capsule and tablet. The time to access Cmax for oral drip is 1 hour, 1.5 hours for tablet and 2.2 hours for capsule, it is shown to be rapid absorption of oral liquid forms.

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. Very small amounts of active substance and its O-desmethyl derivative are found in milk (0.1% and 0.02% of the administered dose, respectively).

Biotransformation:
In humans, tramadol is mainly metabolized 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 urine. Animal experiments have shown that O-desmethyltramadol is 2-4 times stronger than the parent compound. The half-life $t_{1/2,ß}$ (6 healthy volunteers) is 7.9 hours (range 5.4 - 9.6 hours) and is 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 $t_{1/2,\beta}$ is approximately 6 hours, regardless of the route of administration. It can lengthen approximately 1.4 times in patients over the age of 75.

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

Tramadol has a linear pharmacokinetic profile in 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.

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, hematological, clinical chemical and histological examinations showed no evidence of any substance-related changes. Central nervous system symptoms only occurred after high doses significantly above the therapeutic range: restlessness, salivation, convulsions, and decreased weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg, respectively, and dogs tolerated rectal doses of 20 mg/kg without any reaction.

Tramadol doses above a dose of 50 mg/kg/day in rats caused toxic effects in the mother and increased neonatal mortality. Ossification disorders, delay in opening of the vagina and eyes in the offspring in the form of development retardation occurred. Male and female fertility were not affected. Rabbits had toxic effects on the mother above a dose of 125 mg/kg, and skeletal abnormalities in their offspring.

Evidence of mutagenic effects was present in some *in-vitro* test systems. *In-vivo* studies have not shown such effects. According to the information obtained so far, tramadol can be classified as non-mutagenic.

Studies on the tumor-forming potential of Tramadol Hydrochloride have been conducted in rats and mice. Studies in rats have shown 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 in doses above 15 mg/kg) and an increase in pulmonary tumors in all dose groups (no significant, but not dose-dependent) in females.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate.$3H_2O$
Water for injection

6.2. Incompatibilities

Incompatible with diclofenac, indomethacin, phenylbutazone, diazepam, flunitrazepam, midazolam, piroxicam, glyceryltrinitrate solutions for injection.

6.3. Shelf life

24 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. Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

253/42

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First Authorization Date: 20.09.2013
License renewal date:--

10. DATE OF REVISION OF THE TEXT

Calculation of injection volume:

1) Calculation of the total required tramadol hydrochloride dose in mg: body weight (kg) x dose (mg / kg)
2) Calculation of the volume of diluted tramadol hydrochloride solution for injection to be injected: total dose (mg) /appropriate concentration of diluted solution (mg/mL see table below)

So; TRAMOSEL ampoule should be diluted with water for injection. The table below shows what concentrations were obtained (1 mL ampoule contains 50 mg tramadol hydrochloride).

Dilution of TRAMOSEL ampoule

Water for injection	**The resulting concentration**
2 mL + 2 mL	25.0 mg/ mL
2 mL + 4 mL	16.7 mg/ mL
2 mL + 6 mL	12.5 mg/ mL
2 mL + 8 mL	10.0 mg/ mL
2 mL + 10 mL	8.3 mg/ mL
2 mL + 12 mL	7.1 mg/ mL
2 mL + 14 mL	6.3 mg/ mL
2 mL + 16 mL	5.6 mg/ mL
2 mL + 18 mL	5.0 mg/ mL

Sample calculation; For a 45 kg child, when you are asked to be given 1.5 mg of tramadol hydrochloride per weight; it is necessary to administer 67.5 mg of tramadol hydrochloride. For this, 2 mL ampoule is diluted with 4 mL of water for injection; giving a concentration of 16.7 mg of tramadol hydrochloride per mL. 4 mL of diluted solution (approximately 67 mg of tramadol hydrochloride) are then administered.