Package leaflet: Information for the user

Tradol 50 mg/ml Solution for injection or infusion

tramadol hydrochloride

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.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tradol is and what it is used for

Tramadol, the active substance in Tradol, is a painkiller (analgesic) of the opioid group. Its pain alleviating effect is due to its influence on specific nerve cells in the spinal cord and in the brain.

Tradol is used in the treatment of moderate to severe pain.

2. What you need to know before you use Tradol

Do not use Tradol:
- if you are allergic to tramadol or any of the other ingredients of this medicine (listed in section 6)
- if you have acute intoxication with alcohol, sleeping agents, painkillers opioids or other psychotropic agents (medicines which influence mood, emotional status and disposition)
- if you are taking or have taken in the last two weeks, certain medicines called 'monoamine oxidase inhibitors' or MAOIs (used to treat depression). The combination could result in a serious, potentially life-threatening interaction (see 'Other medicines and Tradol').
- if you have epilepsy that is not controlled with your medicine
- as a substitute in drug withdrawal treatment.

Warnings and precautions

Talk to your doctor or pharmacist before using Tradol if you:
- think you may already be dependent on other opioid painkillers
- react sensitively to opiates
- have a consciousness disturbance or are in shock (cold sweat can be an indication of this)
- have difficulty in breathing

• have a head injury or brain diseases that may cause elevated pressure in the skull
• have a liver or kidney disorder
• suffer from epilepsy or seizures (fits) or have had them in the past
• suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see 'Other medicines and Tradol').
There is a small risk that you may experience a so-called serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you have any of the symptoms related to this serious syndrome (see section 4 'Possible side effects').

Sleep-related breathing disorders
Tradol can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

If any of the above applies to you, please talk to your doctor before starting to use this medicine.

Please note that psychological and physical dependence can develop in patients on Tradol. During long-term use, the effects of this medicine may weaken, with the result that it becomes necessary to use a higher dose (development of tolerance). For this reason, Tradol must be used for short periods only and under strict medical supervision in patients at risk of developing drug dependence.

Please also inform your doctor if any of these problems develop while you are using this medicine and if you have experienced such problems in the past.

Extreme fatigue, lack of appetite, severe abdominal pain, nausea, vomiting or low blood pressure. This may indicate that you have adrenal insufficiency (low cortisol levels). If you have these symptoms, contact your doctor, who will decide if you need to take hormone supplement.

Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme and this can affect people in different ways. In some people, they may not get enough pain relief but other people are more likely to get serious side effects. If you notice any of the following side effects, you must stop using this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

Children and adolescents
Use in children with breathing problems
Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Other medicines and Tradol
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

The pain-relieving effect of Tradol may be weakened and/or shortened if you also take medicines containing:
• carbamazepine (used to treat epilepsy)
• ondansetron (prevents nausea).

The risk of side effects increases,

- if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk of having a fit may increase if you take Tradol at the same time. Your doctor will tell you whether Tradol is suitable for you.
- if you are taking certain antidepressants. Tradol may interact with these medicines and you may experience serotonin syndrome (see section 4 'Possible side effects')
- sedative medicines such as tranquillizers, sleeping pills, antidepressants and other pain relievers (morphine, codeine). You may feel excessively drowsy or feel that you might faint.
- medicines that inhibit blood clotting such as warfarin. The dose of these medicines may need to be reduced, otherwise there could be an increased risk of potentially serious bleeding.

Concomitant use of Tradol and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However if your doctor does prescribe Tradol together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Do not use Tradol at the same time as medicines called 'monoamine oxidase inhibitors' (which are used to treat depression), or if you have taken one in the past 2 weeks.

Tradol with food and drink
Do not drink alcohol while using Tradol; this could enhance the effects of the medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy
There is very little information regarding the safety of tramadol in human pregnancy, therefore this medicine should not be used in pregnant women.

Breast-feeding
Tramadol is excreted into breast milk. For this reason, you should not use Tradol more than once during breast-feeding, or alternatively, if you use Tradol more than once, you should stop breast-feeding.

Driving and using machines
This medicine may cause side effects such as drowsiness and dizziness. If this happens, do not drive or use any tools or machines and do not perform any hazardous tasks.

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

3. How to use Tradol

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be used.

The usual doses are given below. Your doctor may gradually increase or decrease your dose depending on how you respond to the treatment. It is important that you do not continue to use this medicine for longer than absolutely necessary.

To open the ampoule allow the solution in the ampoule neck to flow downwards by tapping or shaking. Then firmly holding the ampoule break the ampoule neck away from the coloured spot (that is visible on the ampoule).

1. Glass ampoule, break point under the spot.

2 Place thumb on the spot and snap back.

Adults and adolescents aged 12 years and over:
You will usually have **one injection of 50 mg or 100 mg every 4-6 hours.** If you are in hospital, you may be given Tradol through a drip or you may receive it from a small machine when you push a button. This lets you use Tradol when you feel you need it. Your doctor or nurse will explain how to use the machine.

Children above the age of 1year
The usual single dose is **1 mg to 2 mg per kg bodyweight.** Daily doses of 8 mg per kg bodyweight should not be exceeded.

As a general rule, you should use no more than the minimum dose you require to control your pain. You should not use a dose of more than 400 mg of the active substance daily unless there are specific medical reasons for this.

Children under 1 year:
This medicine is not recommended in children under the age of 1 year.

Elderly patients
In elderly patients (above 75 years) the excretion of tramadol may be delayed. If this applies to you, your doctor may recommend prolonging the dosage interval.

Severe liver or kidney disease (insufficiency)/dialysis patients:
Patients with severe liver and/or kidney insufficiency should not use Tradol without talking to their doctor. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

If you use more Tradol than you should
If you have one dose more than prescribed by mistake, this will not normally have any negative consequences for you. Continue to use Tradol as your pain recurs as usual.
If you have used an excessive dose of the medicine the following signs can occur: pin-point pupils, vomiting (being sick), a fall in blood pressure, rapid heartbeat, collapse, disturbed consciousness

including coma, epileptic fits and difficulties in breathing. If you observe any of these symptoms or if a child accidentally takes this medicine, immediately contact the nearest doctor or hospital for help.

If you forget to use Tradol
You may experience recurrence of pain. Do not use a double dose to make up for a forgotten dose, but continue to take the preparation as prescribed.

If you stop using Tradol
You should not suddenly stop using this medicine unless your doctor tells you to. If you want to stop using your medicine, discuss this with your doctor first, particularly if you have been using it for a long time. Your doctor will advise you when and how to stop, which may be by lowering the dose gradually to reduce the chance of developing unnecessary side effects (withdrawal symptoms) such as restlessness, anxiety, nervousness, insomnia, hyperactivity, tremor or gastrointestinal upset. Other symptoms which have very rarely been seen include panic attacks, severe anxiety, hallucinations, abnormal skin sensations (such as tingling, pins and needles and numbness) and noise in the ears. If you experience any of these side effects when you stop using Tradol, please consult your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side-effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
This medicine can occasionally cause allergic reactions although serious allergic reactions are rare (affects less than 1 in 1,000 people). Tell your doctor straight away if you experience any of the following symptoms of a serious allergic reaction:
- sudden wheezing, difficulty in breathing or dizziness
- swelling of the face or throat.

Other possible side effects
Tell your doctor if any of the following side effects bother you:

Very common (may affect more than 1 in 10 people)
- feeling sick (nausea)
- dizziness.

Common (may affect up to 1 in 10 people)
- headache
- drowsiness
- being sick (vomiting), constipation, dry mouth
- sweating
- fatigue.

Uncommon (may affect up to 1 in 100 people):
- faster, stronger or irregular heartbeat
- collapse or a fall in blood pressure on standing up, which causes dizziness, light-headedness or fainting
- retching, a feeling of pressure in the stomach, stomach bloating
- diarrhoea
- itching, rash and raised, red, itchy skin rash (hives).

Rare (may affect up to 1 in 1,000 people):
- slower heartbeat

- rise in blood pressure
- changes in appetite
- speech disorders
- tingling or numbness in the hands and feet
- tremor
- slow breathing
- epileptic-like seizures
- muscle twitches, uncoordinated movements
- transient loss of consciousness (syncope)
- difficulty sleeping, nightmares
- mood changes
- changes in activity (usually reduced, sometimes increased)
- changes in sensory perception and impairment of the ability to recognise, which can lead to inappropriate decisions
- hallucinations, confusion, delirium
- anxiety
- breathing difficulties
- worsening of asthma has been reported but it has not been established whether it was caused by tramadol
- blurred vision
- dilation or contraction of pupils
- reduced muscle strength
- passing urine with difficulty or pain, producing less urine than normal
- drug dependence (addiction); withdrawal symptoms may occur when treatment is stopped (see 'if you stop using Tradol').

Very rare (may affect up to 1 in 10,000 people):
- blood tests which show changes in the way the liver is working.

Not known (frequency cannot be estimated from the available data):
- decrease in blood sugar level
- hiccups
- serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 2 'What you need to know before you use Tradol').

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance; website: www.hpra. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tradol

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the carton and label after Exp. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tradol contains– The active substance is tramadol hydrochloride.
Each ml of solution for injection or infusion contains 50 mg tramadol hydrochloride
– The other ingredients are sodium acetate trihydrate and water for injections.

What Tradol looks like and contents of the pack
Tradol is available in packs containing 5 ampoules of 1 ml or 2 ml solution.

Not all pack sizes may be marketed.

Tradol is a clear and colourless solution for injection or infusion in a 1 ml or 2 ml ampoule.

Marketing Authorisation Holder
Rowex Ltd., Bantry, Co. Cork, Ireland

Manufacturers
LEK Pharmaceuticals d.d., Verovškova ulica 57, 1526 Ljubljana, Slovenia.
Rowa Pharmaceuticals Ltd., Bantry, Co. Cork, Ireland.
Sandoz GmbH, Biochemiestraße 10, 6250 Kundl, Austria.

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INFORMATION FOR THE HEALTH PROFESSIONAL

Tradol 50 mg/ml Solution for injection or infusion
tramadol hydrochloride

Presentation
Clear glass ampoules containing tramadol hydrochloride 50 mg/ml colourless, aqueous solution.

Excipients: water for injections and sodium acetate trihydrate.

Uses
Indications
Treatment of moderate to severe pain.

Actions
Tradol is a centrally acting opioid analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu 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 (one tenth) to 1/6 (one sixth) that of morphine.

Dosage and 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.Daily doses of 400mg of active substance tramadol hydrochloride should not be exceeded, except in unless there are special clinical circumstances (e.g. tumour pain and severe pain after surgery).

Unless otherwise prescribed, Tradol should be administered as follows:

Adults and adolescents above the age of 12 years:
The usual dosage 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 50-100 mg 4-6 hourly up to a total daily dose of 400 mg.

Children above the age of 1 year:
The recommended single dose of tramadol hydrochloride is 1- 2 mg/kg body weight. The total daily dose of 8 mg tramadol hydrochloride per kg body weight or 400 mg tramadol hydrochloride, whichever is lower, should not be exceeded per day. On account of their high dosage strengths, capsules, prolonged release tablets and dispersible tablets are not intended for children below the age of 12 years.

Elderly patients
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

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

Method of administration
The solution for injection is to be injected slowly or diluted in infusion solution and infused.
It can be administered by intramuscular, intravenous, subcutaneous injection or intravenous infusion.

To open the ampoule allow the solution in the ampoule neck to flow downwards by tapping or shaking. Then firmly holding the ampoule break the ampoule neck away from the coloured spot (that is visible on the ampoule).

1. Glass ampoule, break point under the spot.

2. Place thumb on the spot and snap back.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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 the treatment) to establish whether and to what extent further treatment is necessary.

Contraindications
Tradol is contraindicated
• in hypersensitivity to the active substance or to any of the excipients
• in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products
• in patients who are receiving monoamine oxidase inhibitors or who have taken them within the last 14 days (*see Drug interactions*)
• in patients with epilepsy not adequately controlled by treatment
• for use in narcotic withdrawal treatment

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

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

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

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

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
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

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

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

CYP2D6 metabolism
Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

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

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

Drug Interactions
Tramadol should not be combined 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 on the central nervous system, respiratory and cardiovascular functions have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with tramadol.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects.

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

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic medicinal product, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see contraindications), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied. In a limited number of studies the pre - or post - operative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with post - operative pain.

Fertility, pregnancy and lactation
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on safety of tramadol in human pregnancy. Therefore tramadol should not be used in 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. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

During lactation about 0.1% of the maternal dose is secreted into the milk. Tramadol is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

Breast-feeding
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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

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

Adverse Reactions
Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided.

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

The frequencies are defined as follows: very common >1/10, common ≥1/100, <1/10), uncommon ≥1/1,000, <1/100), rare ≥1/10,000, <1/1,000), very rare (<1/10,000), not known: cannot be estimated from the available data.

Cardiac disorders:
Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia

Investigations:
Rare: increase in blood pressure

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

Metabolism and nutrition disorders:
Rare: changes in appetite
Not known: hypoglycaemia

Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnoea.
Unknown: Hiccups
If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.

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

Nervous system disorders:
Very common: dizziness
Common: headache, somnolence
Rare: paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders
Not known: Serotonin syndrome.

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold.

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 as follows: agitation, anxiety, nervousness, insomnia,

hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Eye disorders:
Rare: miosis, mydrasis, blurred vision

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, constipation, dry mouth
Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Skin and subcutaneous tissue disorders:
Common: hyperhidrosis
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal and connective tissue disorders:
Rare: motorial weakness.

Hepatobiliary disorders:
In a few isolated cases, an increase in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:
Rare: micturition disorders (dysuria and urinary retention)

Immune system disorders:
Rare: Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

General disorders and administration site conditions:
Common: fatigue

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 HPRA Pharmacovigilance; website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

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, conscious disorders up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.

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

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

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tradol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Pharmaceutical Precautions
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with the following infusions fluids:
0.9% Sodium Chloride
0.18% Sodium Chloride and 4% Glucose
5% Glucose
Haemaccel

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

Precipitation will occur if Tradol is mixed in the same syringe with injections of diazepam, non-steroidal anti-inflammatory drugs and anion-forming drugs.

Special precautions for storage
Do not store above 25°C.

Method of sale and supply
Prescription only

Package Quantities
Cartons of 1 ml x 5 ampoules and 2 ml x 5 ampoules

Further information
After intramuscular administration in humans, tramadol is absorbed rapidly and completely: the mean peak serum concentrations (Cmax) is reached after 45 minutes and bioavailability is almost 100%). The half-life of the terminal elimination phase (t½, ß) is 6.0 ± 1.5 h in young volunteers.

Tramadol pharmacokinetics show little age-dependence, the minimal changes being therapeutically irrelevant. In patients above the age of 65 years the t½, ß was 6.5 ± 1.7 h on oral administration. Since Tramadol is eliminated both metabolically and renally, the terminal half-life t½, ß may be prolonged in impaired hepatic or renal function.
However, the increase in the t½, ß values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½, ß Tramadol was a mean of 13.3 ± 4.9 h; in patients with renal insufficiency (creatinine clearance < 5ml/min) it was 11.0 ± 3.2 h.

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