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Tramadol STADA®

Active ingredient
Tramadol hydrochloride

Composition
Each ampoule of 2 ml of injectable solution contains: Tramadol hydrochloride, 100 mg; sodium acetate, water for injection.

Indications
For moderate to severe pain.

Pharmacologic properties
Tramadol hydrochloride is a cyclohexanol derivative with central analgesic and antitussive activities. The drug (and its active M1 metabolite) acts as an opiate agonist, apparently by selective activity at the u-receptor. In addition to opiate agonist activity, Tramadol inhibits reuptake of certain monoamine (norepinephrine, serotonin) which appears to contribute to the drug's analgesic effect. Unlike morphine Tramadol has no respiratory effect over a wide range of analgesic doses. It also does not effect gastrointestinal motility. Its effects on the cardiovascular system are relatively slight.

Pharmacokinetics
Following oral administration (100 gm), tramadol is rapidly and almost completely absorbed. The mean absolute bioavailability of Tramadol after oral administration, irrespective of simultaneous food intake, is 68%; following rectal administration it is 79%, and following i.m. administration 100%. The maximum first-pass effect after oral administration is 30% and after rectal administration 20%.
Tramadol crosses the blood-brain barrier and the placental barrier. It is found in breast milk, together with 0-desmethyl derivative, in very low concentration (0.1% and 0.02% respectively of the administered dose). The elimination half-life t1/2 irrespective of the route of administration, is 5-7 hours. This is slightly prolonged in patients over 65 years of age. Tramadol and its metabolites are almost entirely excreted by the kidney. In the presence of disorders of hepatic and renal function, the half-lives are likely to be somewhat prolonged.

Contra-indications
Tramadol STADA® must not be used in patients with:
- known hypersensitivity to Tramadol
- acute alcohol, analgesic (pain-killer), soporific (sleeping drug), or psychoactive drug intoxication.
- receiving MAOI

Particular caution must be exercised when using Tramadol in any of the following situations:
- opioid dependence
- clouding of consciousness of unclear aetiology
- respiratory centre / respiratory function disturbances
- conditions associated with elevated intracranial pressure, unless mechanical ventilation is provided
- Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

Usage in pregnancy and lactation (ie while breast-feeding)
Tramadol crosses the placental barrier. Animal studies reveal no teratogenic effects. However, as there is a lack of systematic studies, chronic use of Tramadol should be avoided during all three trimesters of pregnancy.
In newborn babies, Tramadol may produce changes in respiratory rate typically with no clinical significance. Tramadol is excreted in the breast milk in a proportion of about 10% of maternal plasma concentrations while breast-feeding. However, a single dosing with Tramadol does not usually necessitate interruption of breast-feeding.

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

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 400mg, 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.

Side effects
Tramadol produces dose-dependent respiratory depression and sedation of varying degree (from mild fatigue to dizziness), but these symptoms do not generally manifest themselves where moderately severe pain is treated with the recommended oral or rectal doses. Nausea, sweating, dry mouth, dizziness, and giddiness may occasionally occur. Effects on the circulation (palpitations, tachycardia, faintness, or circulatory collapse) are possible in rare cases. These adverse effects are particularly liable to occur when the upright position, when the drug is given intravenously, or in patients undergoing physical stress.
In addition, headaches, nausea, vomiting, constipation, gastrointestinal irritation (abdominal pressure, feeling of fullness) and skin reactions (e.g. pruritus, rashes) may rarely occur. Very rare effects include muscular weakness, alterations in appetite, and disturbance in micturition.
On very rare occasions, tramadol shows a variety of psychological side-effects, varying in nature and intensity from individual, depending on personality and duration of treatment. They include alterations in mood (usually elevated but sometimes in gloomy mood, known as dysphoria), alterations in activity (usually suppression, sometimes intensification) and alteration in memory (e.g. decision-taking, disturbances of perception). They have been a few cases of cerebral convulsions. These however, almost always occurred following intravenous administration of high doses of tramadol with concomitant treatment with neuroleptic agents. Allergic reactions extending to shock cannot be reliably ruled out.
Skin-Diaphoresis has been reported in up to 20% of patients treated with oral/parenteral Tramadol.

Postmarketing experience:
Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

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

Undesirable effects

Respiratory depression (rare)

Special precautions for use
Tramadol has a potential for both abuse and dependence. Tramadol is not suitable for use as a substitution drug.
There is a risk of respiratory depression when the recommended parenteral dosage is exceeded, which may occasionally be the case in general anaesthesia. Also, if the recommended dosage is exceeded and or another CNS-depressant drug is being used at the same time, breathing may become depressed.
As the duration of action of the drug is prolonged in patients with impaired liver or kidney function, the dosing interval should be increased, taking account of the pain recurrence pattern as appropriate.
Intravenous Tramadol should be administered by slow intravenous injection.
Caution should be taken in patients with hypersensitivity to morphine – like analgesic, patients with head injury and history of seizures. In patients with myxedema, hypothyroidism or hypoadrenalism, dose reduction may be required.

Effects on ability to drive and use machines
Even when used as directed, tramadol may have such a significant effect on mental alertness that patients should not drive a car or other vehicle nor operate machinery while using Tramadol STADA®.

Interactions with other drugs
Concurrent use of Tramadol and other CNS-depressant drugs and/ or alcohol may enhance the central adverse effects of Tramadol, respiratory depression in particular.

Concomitant treatment with Tramadol and antipsychotic drugs (also called neuroleptics or major tranquilizers) has, on isolated occasions, been associated with epileptic seizures.
The effect of cimetidine (a drug used for treatment of gastric ulcers and gastritis) on the excretion of Tramadol is so small that the resultant changes in analgesic (pain-killing) activity are irrelevant in clinical practice.
Patients treated with MAO inhibitors (drugs for the treatment of mental disorders) within the last 14 days prior to opioid administration have experienced life-threatening interactions with pethidine (another pain killer that belongs to the same group of drugs) on the central nervous system, respiratory and circulatory centres. Similar interactions cannot be ruled out for Tramadol.
Increased incidence of seizures may occur with concomitant administration of Tricyclic Antidepressants, e.g. Cyclobenzaprine MAOI, Selective Reuptake Inhibitors (SSRIs), neuroleptic agents and other drugs that lower the seizure threshold.
Tramadol may potentiate the effects of other CNS depressants (alcohol, sedatives, hypnotic, other centrally acting analgesics, opiate agonists). The drug should be used with caution and dosage of Tramadol may need to be reduced in patients receiving such drugs.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Tramadol STADA® Injection if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT 3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

Warnings and Precautions
Tramadol has a dependence potential. Prolonged use results in the development of tolerance, mental and physical dependence.
Tramadol and other opiods show cross-tolerance.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of setoronin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Tramadol STADA® Injection with serotonergic drugs (See Interaction with Other Medicaments). This may occur within the recommended dosage range.
Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Tramadol STADA® Injection if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/ Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience)

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

Respiratory depression

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

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra-rapid metabolisers. There individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (m1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D26 phenotype varies widely and has been extimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasions, 3% in African Americans and 16-28% in North Afreicans, Ethiopians and Arabs. Data are not available for other ethnic group.

Dosage and administration, duration of therapy

Dosage guide, route and duration of use:

Adults and adolescents (12 years and older)

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

Paediatric population

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

Unless otherwise prescribed, the following guidelines apply:

Tramadol should not in circumstances be used longer than therapeutically absolutely necessary.

If the nature and severity of the disease makes more prolonged analgesic treatment with Tramadol necessary, a regular, careful and frequent check should be carried out possibly by the use of treatment-free intervals to determine whether and to what extent a medical requirement still exists.

Tramadol dosage should be adjusted to the severity and the patient's individual sensitivity. For moderately severe pain, Tramadol should be given the following dosages to adults and juveniles over the age of 14 (single dose):

i.v.: 1 ampoule Tramadol STADA® equivalent to 100 mg Tramadol hydrochloride – inject slowly or infuse diluted in an infusion solution.

i.m.: 1 ampoule Tramadol STADA® equivalent to 100 mg Tramadol hydrochloride.

s.c.: 1 ampoule Tramadol STADA® equivalent to 100 mg Tramadol hydrochloride.

If the analgesic effect is inadequate, a second single dose may be administered after 30-60 minutes. In sever pain, if clinical experience suggests that a higher analgesic requirement can be expected, the higher dose of Tramadol may be used initially.

The recommended dose for postoperative pain is 100 mg initially then 50 mg every 10-20 minutes if necessary during first hour to the total max of 250 mg (including initial dose in first hour, then 50-100 mg every 4-6 hours max. 600 mg daily.

For the treatment of severe postoperative pain, Tramadol doses of up to 500 mg/4h may be used in an on-demand analgesia system. This, however, requires monitoring facilities and special apparatus. In children aged from 1 year upwards, experience to date suggests that Tramadol hydrochloride may be used at doses of 1-2 mg/kg body weight.

The duration of action of Tramadol hydrochloride is on average 4-8 hours, depending on the severity of pain, when the therapeutic doses are given. Daily doses of up to 4 ampoules of Tramadol STADA® (400 mg tramadol hydrochloride) are generally adequate.

The recommended dose for cancer pain is i.m. 300 mg daily in divided doses. When tramadol infusion are used intra-operatively, or in the treatment of tumour-induced pain, however, much higher daily doses have been used.

The duration of action of Tramadol may be prolonged in patients with disorders of renal or hepatic function. The need for dosage alterations in elderly patients is under discussion.

There is some evidence that elderly patients require lower doses of Tramadol than younger patients. Creatinine clearance should be monitored and used as a determining factor for dosage adjustment. Age alone is not sufficient criteria for dosage adjustment.

Approximately 30% of tramadol dose is excreted unchanged in the urine. In patients creatinine clearance less than 30 ml/min the dosing interval of Tramadol should be increased to 12 hours. The maximum recommended daily dose is 200 mg. Since less than 10% of a dose of Tramadol hydrochloride is removed by hemodialysis, patients undergoing

dialysis may receive their usual dosage on the day of dialysis. Adults and children 14 years and older with hepatic cirrhosis may receive a Tramadol hydrochloride dosage of 50 mg every 12 hours.
Notes:
The recommended dosages are guidelines only. In principle, the lowest effective analgesic effective analgesic dose should be chosen. In the treatment of chronic pain, strict time-tabling of doses is preferred.

Symptoms and treatment for overdosage and antidote
The following typical symptoms of overdosage have been observed: disturbances of consciousness, extending to coma; generalised epileptic fits, hypertension, tachycardia, constricted or dilated pupils, respiratory depression extending to respiratory arrest.
These effects can be abolished by administration of an opiate antagonist (e.g. naloxone), which should be administered cautiously in repeated small doses, since its duration of action is shorter than that of Tramadol. In addition, intensive-care measures (particularly incubation and ventilation) should also be introduced. If fits occur, the use of benzodiazepines should be considered, In addition, measures to prevent heat loss, and volume replacement therapy may be required. In oral intoxication with Tramadol, gastric lavage may be useful. Some manifestations of overdosage, eg. Seizures, may not be reversible with an opiate antagonist eg Naloxone.

Shelf life
Do not use after the expiry date shown on the package.
Shelf life is 5 years in normal condition.
Do not store above 30°C.
Keep this and other drugs away from reach of children.

Packaging
Tramadol STADA® is a clear, colourless solution available in packs of 5 ampoules of 2 ml injectable solution, 10 ampoules of 2 ml injectable solution and 20 ampoules of 2 ml injectable solution. Not all sizes are available in certain countries.

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