PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Tramadol Injection 50 mg/ml Pharma-Q solution for injection

Tramadol Injection 100 mg/2 ml Pharma-Q solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution contains tramadol hydrochloride 50 mg.

Each 2 ml solution contains tramadol hydrochloride 100 mg.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless liquid filled in clear glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to moderately severe pain.

4.2 Posology and method of administration

Posology

The dosage should be adjusted to the intensity of pain and the individual's response to the analgesic action of Tramadol Injection Pharma-Q.

Tramadol Injection Pharma-Q should not be used to treat minor pain.

Unless otherwise prescribed, Tramadol Injection 100 mg/2 ml Pharma-Q ampoules should be administered as follows:

Single dose for adults and children over 12 years of age

IV: 1 ampoule (100 mg/2 ml - injected slowly or diluted in solution for infusion and infused)

IM: 1 ampoule (100 mg/2 ml)

SC: 1 ampoule (100 mg/2 ml)

In general a total daily dose should not exceed 400 mg of tramadol (equivalent to 4 ampoules). Intravenous injection must be given slowly over 2 - 3 minutes.

For postoperative pain

Administer an initial bolus of 100 mg. During the 90 minutes following the initial bolus, further doses of 50 mg may be given every 30 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg or 100 mg 4 - 6 hourly up to a total daily dose of 400 mg.

For less severe pain

Administer 50 mg or 100 mg 4 - 6 hourly.

Children

Tramadol Injection Pharma-Q is not suitable for children under the age of 12 years.

Elderly patients

The usual dosages may be used except in patients 75 years of age and over where a downward adjustment of the dose and/or prolongation of the interval between doses are recommended.

Renal impairment/renal dialysis

The elimination of tramadol may be prolonged. It is recommended that the usual initial dosage be used. For patients with a creatinine clearance < 30 ml/min, the dosage interval should be increased to 12 hours. As tramadol is removed very slowly by haemodialysis or

haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment

The elimination of tramadol may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Method of administration

The Tramadol Injection Pharma-Q is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient-controlled analgesia. For instructions for use and handling of the medicine before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to tramadol hydrochloride or to any of the excipients of Tramadol Injection Pharma-Q (see section 6.1).
- Tramadol Injection Pharma-Q should not be given to patients suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines.
- Tramadol Injection Pharma-Q should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5).
- Tramadol Injection Pharma-Q is contraindicated in patients with epilepsy not adequately controlled by treatment.
- Tramadol Injection Pharma-Q must not be used in narcotic withdrawal treatment.
- Pregnancy and breastfeeding (see section 4.6).
- All children younger than 12 years of age (see section 4.2 and 4.4).

- Tramadol Injection Pharma-Q should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.
- Tramadol Injection Pharma-Q should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

4.4 Special warnings and precautions for use

At therapeutic doses, Tramadol Injection Pharma-Q has the potential to cause withdrawal symptoms. Cases of dependence and abuse have been reported.

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8 000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

Tolerance, psychic and physical dependence (of the morphine-type) may develop, especially after long-term use. When a patient no longer requires therapy with Tramadol Injection Pharma-Q, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Tramadol Injection Pharma-Q is not a suitable substitute in opioid dependent patients (see section 4.3). Tramadol Injection Pharma-Q does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Tramadol Injection Pharma-Q may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected (see section 4.7).

Concomitant use of Tramadol Injection Pharma-Q and sedating medicines such as benzodiazepines or related substances, may result in respiratory depression, sedation, coma and death. Concomitant prescribing with these sedating medicines should be only undertaken where no other option is available. If concomitant prescribing is the only option, the lowest effective dose of Tramadol Injection Pharma-Q should be used, and duration of concomitant treatment should be as short as possible. Patients should be monitored closely for signs and symptoms of respiratory depression and sedation. It is recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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.

Tramadol Injection Pharma-Q should not be used in the treatment of minor pain.

Children: Tramadol Injection Pharma-Q is not suitable for children under the age of 12 years.

Warnings against 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 life-threatening adverse events.

Children with compromised respiratory function, due to neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures have factors which may worsen symptoms of opioid toxicity.

Other precautions

Tramadol Injection Pharma-Q should be used with caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. In patients sensitive to opiates Tramadol Injection Pharma-Q should only be used with caution (see section 4.3).

Convulsions have been reported in patients receiving Tramadol Injection Pharma-Q at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg). Patients with a history of epilepsy or those susceptible to seizures should only be treated with Tramadol Injection Pharma-Q if there are compelling reasons (see section 4.3).

The risk of convulsions may increase in patients receiving Tramadol Injection Pharma-Q and concomitant medicines that can lower the seizure threshold (see section 4.5).

The risk of seizures may also be increased in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal and intracranial infections, head trauma, metabolic disorders, and naloxone treatment with tramadol overdose.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant medicines are being administered, or if the recommended dosage is significantly exceeded, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol was reported to enhance intra- operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed; Tramadol Injection Pharma-Q may be used intra-operatively in the same way as other analgesic agents are routinely used.

4.5 Interaction with other medicines and other forms of interaction

Tramadol Injection Pharma-Q should not be combined with MAO inhibitors (see section 4.3).

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 function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol Injection Pharma-Q.

The concomitant use of opioids with sedating medicines such as benzodiazepines or related products increases the risk of respiratory depression, sedation, coma and death because of additive CNS depressant effect.
The dose of Tramadol Injection Pharma-Q and the duration of the concomitant use should be limited (see section 4.4).

Concomitant administration of Tramadol Injection Pharma-Q with other centrally acting medicines, including alcohol, may potentiate CNS depressant effects (see section 4.5 and 4.8).

Tramadol Injection Pharma-Q 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 medicines (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

Concomitant therapeutic use of Tramadol Injection Pharma-Q and serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus,
- Inducible or ocular clonus with agitation or diaphoresis,
- Tremor and hyperreflexia,

- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR with major bleeding and ecchymoses in some patients and so care should be taken when commencing treatment with Tramadol Injection Pharma-Q in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.

Carbamazepine – The simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore, no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25 % increase in the tramadol C_{max} and AUC; T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

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 (see section 4.8).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Tramadol Injection Pharma-Q is contraindicated in pregnancy.

Animal studies with tramadol have revealed effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta.

Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

Approximately 0,1 % of the maternal dose of tramadol is excreted in breast milk. Tramadol Injection Pharma-Q should not be administered during breast-feeding or alternatively, breast-feeding should be discontinued during treatment with tramadol. After a single administration of Tramadol Injection Pharma-Q however, it is not usually necessary to interrupt breast feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Tramadol Injection Pharma-Q may cause somnolence and dizziness and these effects may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

Tramadol Injection Pharma-Q can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

a. Summary of the safety profile

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided. The most frequently reported adverse drug reactions are nausea and dizziness, both occurring in more than 10 % of patients.

b. Tabulated summary of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
Metabolism and nutrition disorders	Less frequent	Changes in appetite.
	Frequency unknown	Hypoglycaemia.
Psychiatric disorders	Less frequent	Hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic side effects may occur following administration of tramadol, which vary individually in intensity and nature (depending on personality and duration of

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
		medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.
Nervous system disorders	Frequent	Dizziness, headache, somnolence.
	Less frequent	Changes in appetite, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.
Eye disorders	Less frequent	Blurred vision, miosis, mydriasis.
Cardiovascular system disorders	Less frequent	Cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially after intravenous administration and in patients who are physically stressed. Bradycardia.
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory depression, dyspnoea.

MedDRA System Organ Class	**Frequency**	**Adverse reactions**
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation, dry mouth.
	Less frequent	Retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.
Hepato-biliary disorders	Less frequent	Increases in liver enzyme values.
Skin and subcutaneous tissue disorders	Frequent	Sweating.
	Less frequent	Dermal reactions (e.g. pruritus, rash, urticaria).
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle weakness.
Renal and urinary system disorders:	Less frequent	Micturition disorders (difficulty in passing urine, dysuria and urinary retention).
General disorders and administrative site conditions	Frequent	Fatigue.
Investigations	Less frequent	Increase in blood pressure.

c. Description of selected adverse reactions

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and

gastrointestinal symptoms. Other symptoms that have been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, personalisation, derealisation, paranoia).

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.4 and 4.5).

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur. Worsening of asthma has been reported, though a causal relationship has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

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. If naloxone is to be administered, use cautiously because it may precipitate seizures. Convulsions should be treated with intravenous diazepam. Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute tramadol intoxication with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code N 02A X02: Analgesics – other opioids

Tramadol is a centrally acting analgesic with binding to specific opioid receptors. It is a non-selective, pure agonist at mu (μ), delta (8) and kappa (k) opioid receptors with a higher affinity for the μ receptor. Other mechanisms, which may contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline and serotonin. Tramadol does not promote the release of histamine.

5.2 Pharmacokinetic properties

Tramadol is well absorbed after oral or rectal administration, with an absorption half-life (t ½ ka) of 0,38 ± 19 0,18 hours, leading to an analgesic effect lasting for up to 9 hours. The parenteral form of Tramadol has a more rapid onset of action. The mean systemic bioavailability is 68 %.

Tramadol hydrochloride crosses the blood-brain and placental barrier. Only very small amounts are excreted in breast milk unchanged or as the metabolite MI (tramadol hydrochloride approximately 0,1 %, MI approximately 0,02 % of the i.v. dose). The

elimination half-life is 5 to 7 hours. Tramadol is mainly metabolised in the liver (90 %). Tramadol hydrochloride and its metabolites are almost completely excreted by the renal route

(95 %). Biliary excretion of these components is quantitatively insignificant and is therefore subject to hepatic metabolism and renal elimination. The terminal half-life (tp) is likely to be prolonged in impaired hepatic or renal function. The increase in the (tp) value is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis, the mean tp of tramadol was 13,3 ± 4, 9 h, t½, p/M1 18,5 ± 9,4 h, in patients with renal insufficiency (creatinine clearance ± 5 ml/ min) the values were 11,0 ± 3,2 h (tramadol) and 16,9 ± 3,0 h (M1) respectively.

There are sex differences in the pharmacokinetic parameters of tramadol. The absolute bioavailability was 73 % in males and 79 % in females. Plasma clearance was 6,4 ml/min/kg in males and 5,73 ml/min/kg in females following a 100 mg IV dose. Following a single oral dose and after adjusting for bodyweight, females had a 12 % higher peak concentration and a 35 % higher area under the concentration time curve compared to males. The clinical significance of these differences is unknown.

5.3 Preclinical safety data

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate

Water for injection

6.2 Incompatibilities

Precipitation will occur if Tramadol 50mg/ml Solution for Injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indometacin, midazolam and piroxicam. Tramadol 50mg/ml Solution for Injection must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 °C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C in a cool dry place.

6.5 Nature and contents of container

Tramadol Injection 50 mg/ml Pharma-Q is packed in a 2 ml clear glass type 1 ampoule with green snap-off.

Tramadol Injection 100 mg/2 ml Pharma-Q is packed in a 2 ml clear glass type 1 ampoule with red snap-off.

Pack sizes: 1, 2, 5, 10 or 20 ampoules per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The prepared infusion solution should be made up immediately before use.

Tramadol Injection Pharma-Q is physically and chemically compatible for up to:

- 24 hours with 4,2 % sodium bicarbonate and Ringer's solution.

Or up to 5 days with the following infusion solutions:

- 0,9 % sodium chloride
- 0,18 % sodium chloride and 4 % glucose
- sodium lactate compound
- 5 % glucose

7 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

50 Commando Road

Industria West, 2093

Johannesburg

8 REGISTRATION NUMBERS

Tramadol Injection 50 mg/ml Pharma-Q: 47/2.9/1178

Tramadol Injection 100 mg/2 ml Pharma-Q: 47/2.9/1179

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2022

10 DATE OF REVISION OF THE TEXT

09 July 2024