1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TRAMASPEN SR 100 mg sustained release tablets

TRAMASPEN SR 150 mg sustained release tablets

TRAMASPEN SR 200 mg sustained release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of TRAMASPEN SR 100 mg contains 100 mg tramadol hydrochloride.

Contains sugar: Lactose monohydrate 2,52 mg

Each tablet of TRAMASPEN SR 150 mg contains 150 mg tramadol hydrochloride.

Contains sugar: Lactose monohydrate 2,52 mg

Each tablet of TRAMASPEN SR 200 mg contains 200 mg tramadol hydrochloride.

Contains sugar: Lactose monohydrate 2,52 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sustained release tablets.

TRAMASPEN SR 100 mg: Round, white coloured film-coated tablet debossed with "E95" on one side and plain on the other side.

TRAMASPEN SR 150 mg: Round, pale orange coloured film-coated tablet debossed with "E96" on one side and plain on the other side.

TRAMASPEN SR 200 mg: Round, brownish orange coloured film-coated tablet debossed with "E97" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TRAMASPEN SR is indicated in adults and children aged 12 years and older for the management of moderate to severe pain.

4.2. Posology and method of administration

Posology

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient.

Adults and children over 12 years

The usual initial dose is 100 mg twice daily, to be taken whole, not divided or chewed, with sufficient liquid, with or without meals, preferably mornings and evenings. If pain relief is not adequate, the dose may be increased to 150 mg or 200 mg twice daily.

A total daily dose of 400 mg TRAMASPEN SR should not be exceeded.

Dosage intervals can be adjusted to individual requirements but should be at least 8 hours. The lowest analgesically effective dose should generally be selected.

Duration of treatment

Under no circumstances should TRAMASPEN SR be given for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment with TRAMASPEN SR, careful checks should be carried out initially and at regular intervals to assess efficacy and adverse events, and to what extent further treatment is necessary.

Special populations

Elderly population

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended in the elderly (over 75 years).

Renal insufficiency/dialysis/hepatic insufficiency

In patients with renal and/or hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency, TRAMASPEN SR is not recommended.

Paediatric population

Children below 16 years of age

The use of TRAMPASPEN SR is contraindicated in children below 12 years of age (see 18 section 4.3)

Method of administration

For oral administration.

4.3. Contraindications

TRAMASPEN SR is contraindicated in:

- Patients with hypersensitivity to tramadol hydrochloride, opioids or to any excipients in TRAMASPEN SR (see section 6.1).
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines (due to the risk of respiratory depression).

- Patients who are receiving monoamine oxidase inhibitors (MAOIs) or within two weeks of their withdrawal (see section 4.5).
- Patients with epilepsy not adequately controlled by treatment.
- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions (see section 4.4).
- Patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- Pregnancy and lactation (see section 4.6).

TRAMASPEN SR is contraindicated in children younger than 12 years of age.

TRAMASPEN SR must not be used for narcotic withdrawal treatment.

4.4. Special warnings and precautions for use

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, TRAMASPEN SR should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain.

Hazardous and harmful use

TRAMASPEN SR poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.9).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of TRAMASPEN SR. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see sections 4.3 and 4.9).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol (see section 4.5)

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking TRAMASPEN SR.

TRAMASPEN SR should be used with care in patients with increased reactivity to opioids.

Seizures

Seizures have been reported in patients receiving TRAMASPEN SR at dosages within the recommended dosage range. The risk of seizures may be enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re-uptake inhibitors, MAOIs and neuroleptics. The risk of seizures may also be increased in patients with epilepsy; with a history of seizures or in patients with a recognized risk for seizures e.g. medicine and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with TRAMASPEN SR overdose. Patients with epilepsy or those susceptible to seizures should only be treated if there are compelling circumstances.

TRAMASPEN SR may increase the seizure risk in patients taking neuroleptics and other medicines that lowers the seizure threshold (see section 4.5).

Drug abuse and dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop. Tramadol, as contained in TRAMASPEN SR, has been associated with craving drug-seeking behaviour and tolerance development and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed TRAMASPEN SR at recommended doses. Cases of abuse and dependence on TRAMASPEN SR have been reported. TRAMASPEN SR should not be used in opioid-dependent patients. TRAMASPEN SR can reinstate physical dependence in patients that have tendency to drug abuse, a history of drug dependence or who are chronically using opioids. There is an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.

For such patients, treatment with TRAMASPEN SR is not recommended.

Minor pain

TRAMASPEN SR should not be used in the treatment of minor pain (see section 4.1).

Hepatic and renal function impairment

TRAMASPEN SR should be used with caution in patients with impairment of hepatic and renal function and in patients with convulsive disorders or in shock (see section 4.2).

Impaired consciousness of unclear aetiology, shock

TRAMASPEN SR should only be used following a strict benefit-risk evaluation and appropriate precautionary measures in impaired consciousness of unclear aetiology or shock.

Risk from concomitant use of sedative medicines such as benzodiazepines or related active substances (see section 4.5)

Concomitant use of opioids, such as tramadol, and sedative medicines such as benzodiazepines, related active substances, or other CNS depressant, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of TRAMASPEN SR with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-acting antiemetics and other CNS depressants, should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe TRAMASPEN SR concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be monitored closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.

Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking TRAMASPEN SR (see section 4.5).

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated

or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see *Hazardous and harmful use*, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see *Ceasing Opioids* below).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate (see section 4.8).

When discontinuing TRAMASPEN SR in a person who may be physically-dependent, the medicine should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids* below).

Opioid-induced hyperalgesia or Allodynia

Opioid-induced hyperalgesia (OIH) is a paradoxical response to an opioid, such as TRAMASPEN SR, in which there is an increased level of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. It differs from tolerance *(see Tolerance, dependence and withdrawal),* in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalised pain (i.e. less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of TRAMASPEN SR should be reduced or tapered off, if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms, uncontrolled pain, psychological distress and suicide (see *Tolerance, dependence and withdrawal*).

Such symptoms may lead the patient to seek other sources of licit or illicit opioids, such as heroin and other substances.

Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any serious withdrawal symptoms, increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 % to 25 % every 2 to 4 weeks. If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until the patient is stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medicine-assisted treatment and/or referral to a specialist should be considered.

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. Even at labelled dosage regimens, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience signs of toxicity such as extreme sleepiness, confusion, or shallow breathing (see section 4.9).

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.

Serotonin syndrome

TRAMASPEN SR alone or in combination with other serotonergic medicines may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.5, 4.8 and 4.9).

In the case of concomitant treatment with other serotonergic medicines, 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 medicines usually brings about a rapid improvement.

Adrenal insufficiency

Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol. Cortisol helps the body respond to stress.

Decreased sex hormone levels

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility (see section 4.6).

Risk of addiction

There is an increased risk of addiction to TRAMASPEN SR in patients with a personal or family history of substance abuse or mental health disorders.

Hyponatraemia

Hyponatraemia may occur with the use of TRAMASPEN SR, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines that may cause hyponatraemia. This hyponatraemia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolves with discontinuation of TRAMASPEN SR and appropriate treatment (e.g. fluid restriction). During TRAMASPEN SR treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Other conditions

TRAMASPEN SR should be used with caution in patients with hypothyroidism, prostatic hyperplasia, hypotension, inflammatory or obstructive bowel disorders or myasthenia gravis.

Paediatric population

Accidental ingestion/exposure

Accidental ingestion or exposure of TRAMASPEN SR, especially by children, can result in a fatal overdose of tramadol. Patients and their caregivers should be given information on safe storage and disposal of unused TRAMASPEN SR (see sections 6.4 and 6.6).

Post-operative use in children

There have been reports in the published literature that tramadol, as contained in TRAMASPEN SR, given post-operatively in children (under 18 years of age) after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to life threatening adverse events (see section 4.3).

Cautions against use in children and adolescents under 18 years of age

TRAMASPEN SR is contraindicated for children under the age of 12 years.

Caution is advised against use of TRAMASPEN SR in adolescents between 12 and 18 years of age who are obese, have obstructive sleep apnoea syndrome, or have serious lung disease.

Children with compromised respiratory function

TRAMASPEN SR is not recommended for use in children in whom respiratory function may 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.

Excipients

TRAMASPEN SR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TRAMASPEN SR.

4.5. Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

TRAMASPEN SR should not be combined with MAOIs (see section 4.3).

In patients treated with MAOIs 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 MAOIs cannot be ruled out during treatment with TRAMASPEN SR (see section 4.3).

Concomitant administration of TRAMASPEN SR with other centrally depressant medicines including alcohol may potentiate the CNS effects (see section 4.4). The duration of anaesthesia may be prolonged when TRAMASPEN SR is combined with barbiturates.

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and TRAMASPEN SR is not advisable, because the analgesic effect of a pure agonist like TRAMASPEN SR may be reduced in such circumstances.

TRAMASPEN SR can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, anti-psychotics and other seizure threshold-lowering medicines (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions (see sections 4.3 and 4.4).

There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol, as contained in TRAMASPEN SR, in combination with other serotoninergic medicines, such as lithium, selective serotonin re-uptake inhibitors (SSRIs) or with MAOIs and migraine medicines (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4, 4.8 and 4.9).
Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.
Withdrawal of the serotoninergic medicines usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Caution should be exercised during concomitant treatment with TRAMASPEN SR and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.
The action of warfarin on blood clotting may be affected and small areas of bleeding under the skin may appear when used in combination with TRAMASPEN SR.

CYP2D6 inhibitors (such as amitriptyline, fluoxetine, paroxetine) and 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.

CYP3A4 inducers (such as rifampicin and St John’s wort) may induce the metabolism of tramadol (N-demethylation) and the metabolism of the active O-demethylated metabolite, reducing the therapeutic effect.

In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT_3 antagonist ondansetron increased the requirement of TRAMASPEN SR in patients with postoperative pain. TRAMASPEN SR may decrease the antiemetic efficacy of ondansetron.

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

Based on available pharmacokinetic results, no clinically relevant interactions are expected with the co-administration or previous administration of tramadol, as contained in TRAMASPEN SR, with cimetidine (enzyme inhibitor).

4.6. Fertility, pregnancy and lactation

TRAMASPEN SR is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

TRAMASPEN SR should not be used in pregnant women. TRAMASPEN SR crosses the placenta. Animal studies with TRAMASPEN SR revealed at very high doses effects on organ development, ossification and neonatal mortality.

The repeated administration of TRAMASPEN SR during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3).

Breastfeeding

TRAMASPEN SR is not recommended during breastfeeding.

Tramadol and its active form are also present in breast milk.

There is risk of serious adverse reactions in breastfed infants. These adverse reactions include excess sleepiness, difficulty breastfeeding or serious breathing problems that could result in death.

Fertility

Post marketing surveillance does not suggest an effect of tramadol, as in TRAMASPEN SR, on fertility. Animal studies did not show an effect of tramadol on fertility.

Patients should be advised to inform their healthcare providers if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility. Healthcare providers should conduct laboratory evaluation in patients presenting with such signs or symptoms.

4.7. Effects on ability to drive and use machines

TRAMASPEN SR has major influence.

TRAMASPEN SR may cause drowsiness and blurred vision altering one's capacity to react, so that the ability to drive and use machines or work without a steady foothold is reduced. This applies especially at the start of treatment, when changing over to another treatment, in combination with other centrally active medicines, and particularly if combined with alcohol (see section 4.5).

TRAMASPEN SR can impair cognitive function and can affect a patient's ability to drive safely.

4.8. Undesirable effects

a) Summary of the safety profile

The common side-effects during treatment with TRAMASPEN SR are nausea and dizziness both occurring in more than 10% of patients.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Immune system disorders	Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema), anaphylaxis	Angioedema	
Metabolism and nutrition disorders	Anorexia	Changes in appetite	Hypoglycaemia
Psychiatric disorders	Depression	Hallucinations, confusion, sleep disorders, anxiety and nightmares, psychic adverse reactions. Their intensity and nature may vary (according to the patient's personality and length of therapy). These may appear as a change in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), cognitive and sensory perception (decision behaviour, perception disorders), dependence, delirium.	
Nervous system disorders	Dizziness, sedation, vertigo, headaches, somnolence	Paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders, hypaesthesia, amnesia, abnormal gait, abnormal sensation, trembling	Serotonin syndrome
Eye disorders		Blurred vision, miosis, mydriasis	
Cardiac disorders		Cardiovascular regulation (palpitation, tachycardia), bradycardia, increase in blood pressure, dysrhythmia, chest pain, myocardial infarction.	

Vascular disorders		Cardiovascular regulation (postural hypotension or cardiovascular collapse), flushing, fainting	
Respiratory, thoracic and mediastinal disorders		Respiratory depression, dyspnoea, worsening of asthma, rhinorrhoea, nasal congestion, bronchospasm, respiratory depression in children	Slow breathing, bronchitis,
Gastrointestinal disorders	Nausea, vomiting, constipation, dry mouth, dyspepsia, diarrhoea, abdominal pain	Retching, gastrointestinal irritation (e.g. feeling of pressure in stomach, bloating), hiccups, appendicitis, cholecystitis, cholethiasis, pancreatitis.	
Hepato-biliary disorders		Increase in liver enzyme values (ALT and AST).	
Skin and subcutaneous tissue disorders	Hyperhidrosis, dermal reactions (e.g. pruritis, skin rash)	Dermal reactions (e.g. itching, rash, urticaria), Stevens-Johnson syndrome, toxic epidermal necrolysis, vesicles, cellulitis, dermatitis.	
Musculoskeletal and connective tissue disorders		Muscle weakness, arthralgia, myalgia, joint stiffness or swelling, back pain	
Renal and urinary disorders		Micturition disorders (difficulties in passing urine, dysuria, urinary retention, urinary frequency and haematuria)	
General disorders and administrative site conditions	Fatigue, influenza-like illness, asthenia	Hypothermia (rigors)	

Post-marketing

System organ class	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Nervous system disorders		Speech disorders
Eye disorders		Mydriasis
Gastrointestinal disorders	Increased risk of abdominal pain, including pancreatitis	

c) Description of selected adverse reactions

Cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse) may appear in patients who are physically stressed.

Epileptic convulsions occurred mainly after taking high doses of TRAMASPEN SR or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.3 and 4.4).

Dependence may occur (see section 4.4). After discontinuation of TRAMASPEN SR, signs of withdrawal may appear. Symptoms of withdrawal reactions 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).

Hyponatraemia:

Hyponatraemia and/or SIADH may occur with TRAMAZAC SR, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medicines that may cause hyponatraemia (see section 4.4).

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. Healthcare providers are asked to report any suspected adverse reactions to: SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

In principle, on intoxication with TRAMASPEN SR, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular constriction of the pupil of the eye, vomiting, slow heartbeat, hypotension cardiovascular collapse, weakness, consciousness disorders, coma, convulsions, cold clammy skin, dizziness, rhabdomyolysis progressing to renal failure, respiratory depression up to respiratory arrest.

Serotonin syndrome has also been reported (see section 4.4).

Treatment

The general emergency measures apply. Keep the airway open, prevent aspiration and maintain respiration and circulation.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone).

Treatment of restlessness is symptomatic and supportive.

In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In cases of overdosage with oral formulation, gastrointestinal decontamination with activated charcoal is only recommended within 2 hours after TRAMASPEN SR intake. Gastrointestinal decontamination at a later time point may be useful in case of overdosage with exceptionally large quantities or prolonged-release formulations.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with TRAMASPEN SR with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A.2.9 Other analgesics

Pharmacotherapeutic group: Analgesics, other opioids.

ATC code: N02AX02

Mechanism of action

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

Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably.

5.2. Pharmacokinetic properties

Absorption

Tramadol hydrochloride is readily absorbed following oral administration. Oral bioavailability 21 is approximately 68 % after a single dose and increases to 90 % at steady state. Onset of 22 action is dose dependent but generally occurs within one hour of dosing, peaking within 2 to 23 3 hours. Duration of analgesia is about 6 hours. The rate or extent of absorption is not 24 significantly affected by co-administration with food.

Distribution

C_{max} (141 ± 40 ng/mL) is reached 4,9 hours after oral administration of TRAMASPEN SR 100 mg and 4,8 hours (C_{max} 260 ± 62 ng/mL) after oral administration of TRAMASPEN SR 200 mg.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The elimination half-life is 5 to 7 hours.

Biotransformation

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 quantitively insignificant and is therefore subject to hepatic metabolism and renal elimination. The terminal half-life ($t_{1/2}$) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean $t_{1/2}$ of tramadol was 13,3 ± 4,9 h, $t_{1/2}$ /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.

Elimination

The elimination half-life (t½ β) of tramadol is about 6 hours, irrespective of the method of administration. In patients over 75 years of age, elimination half-life may be prolonged by a factor of approximately 1,4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

TRAMASPEN SR 100 mg:

Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, Opadry II White (coating material).

Opadry II White contains hypromellose (E464), lactose monohydrate, macrogol (E1521), propylene glycol (E1520), talc (E553b), titanium dioxide (E171).

TRAMASPEN SR 150 mg:

Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, Opadry II Beige (coating material).

Opadry II Beige contains hypromellose (E464), iron oxide red (E172), lactose monohydrate, macrogol (E1521), propylene glycol (E1520), quinoline yellow aluminium lake (E104), talc (E553b), titanium dioxide (E171).

TRAMASPEN SR 200 mg:

Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, Opadry II Pink (coating material).

Opadry II Pink contains hypromellose (E464), iron oxide red (E172), iron oxide yellow (E172), lactose monohydrate, macrogol (E1521), propylene glycol (E1520), talc (E553b), titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.3. Special precautions for storage

Store at or below 25 °C.

6.4. Nature and contents of container

PVC/PVDC/Aluminium blisters or PVC/PE/PVDC/Aluminium blisters with 10 tablets per blister strip.

TRAMASPEN SR 100 mg and 150 mg:

1, 3, 6 or 10 blister strips and a package insert are packed in a carton. Pack sizes of 10, 30, 60 or 100 tablets.

TRAMASPEN SR 200 mg:

6 blister strips and a package insert are packed in a carton. Pack size of 60 tablets.

Not all packs or pack sizes may be marketed.

6.5. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Tel: 0800 122 912

8. REGISTRATION NUMBER

TRAMASPEN SR 100 mg - 51/2.9/2000

TRAMASPEN SR 150 mg - 51/2.9/2001

TRAMASPEN SR 200 mg - 51/2.9/2002

9. DATE OF FIRST AUTHORISATION

18 May 2022

10. DATE OF REVISION OF TEXT

08 July 2026

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.