PACKAGE INSERT FOR TRAMASAC SR 100, 150 AND 200

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

TRAMAZAC SR 100 film coated tablet

TRAMAZAC SR 150 film coated tablet

TRAMAZAC SR 200 film coated tablet

COMPOSITION

Active ingredient:

Each **TRAMAZAC SR 100** tablet contains 100 mg tramadol hydrochloride.

Each **TRAMAZAC SR 150** tablet contains 150 mg tramadol hydrochloride.

Each **TRAMAZAC SR 200** tablet contains 200 mg tramadol hydrochloride.

Inactive ingredients:

Magnesium stearate, microcrystalline cellulose, polyethylene oxide, povidone K-30, Opadry Orange 03F53885 (for **TRAMAZAC SR 150**), Opadry Pink 03F84640 (for **TRAMAZAC SR 200**), and Opadry White 03F58750 (for **TRAMAZAC SR 100**).

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 2.9. Other analgesics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. It is a non-selective, pure agonist at mu (μ), delta (δ) and kappa (κ) 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 enhancement of serotonin release.

Tramadol hydrochloride does not promote histamine release.

Pharmacokinetic properties:

Tramadol hydrochloride is readily absorbed following oral administration and is mainly subject to first-pass metabolism in the liver (90 %). Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4, CYP2D6, glucuronidation or sulphation in the liver. The metabolite *O*-desmethyl-tramadol is pharmacologically active.

Oral bioavailability is approximately 68 % after a single dose and increases to 90 % at steady state. Onset of action is dose dependent but generally occurs within one hour of dosing, peaking within 2 to 3 hours. Duration of analgesia is about 6 hours. The rate or extent of absorption is not significantly affected by co-administration with food.
Tramadol hydrochloride and its metabolites are almost completely excreted in the urine. The elimination half-life is 5 to 7 hours, but is prolonged in impaired hepatic and renal function.

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

INDICATIONS

TRAMAZAC SR is indicated for the management of moderate to moderately severe pain.

CONTRAINDICATIONS

- Hypersensitivity to tramadol hydrochloride or opioids or to any excipients in **TRAMAZAC SR** (see **COMPOSITION**).

- Acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines (due to the risk of respiratory depression).
- Patients taking monoamine oxidase (MAO) inhibitors or within two weeks of their discontinuation (see **INTERACTIONS**).
- Narcotic withdrawal treatment.
- Respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.
- Increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
- Pregnancy and lactation.
- **TRAMAZAC SR** is not suitable for children under the age of 12 years.

WARNINGS AND SPECIAL PRECAUTIONS

Epileptic fits may occur after taking high doses of **TRAMAZAC SR** or when medicines that may cause fits or lower fit threshold were taken at the same time.

Use with caution in patients with a history of epilepsy as the risk of seizures is increased if **TRAMAZAC SR** is used with other medicines that have the potential to reduce the seizure threshold.

Avoid the use of **TRAMAZAC SR** in patients with a history of addiction, as physical dependence of the morphine-type may develop. Reinstatement of physical dependence in patients that have previously been dependent may occur with **TRAMAZAC SR**.
TRAMAZAC SR should not be used in patients who are suicidal.

TRAMAZAC SR should be given with caution in opioid dependence, reduced level of consciousness of uncertain origin, disorders of the respiratory function, patients with

hypothyroidism, adrenocortical insufficiency, asthma, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

The use of **TRAMAZAC SR** concurrently with other central nervous system medicines is likely to intensify and prolong CNS effects (see **INTERACTIONS**).
The possibility of respiratory depression cannot be excluded if the recommended dose is exceeded or other centrally depressant medicines are given concomitantly.

At the end of medication, signs of withdrawal may occur (including abdominal pain, seizures, nervousness, shaking, nausea, vomiting, sweats).

Use with caution in patients with renal or hepatic impairment and avoid if severe.

TRAMAZAC SR should not be used in the treatment of minor pain.

Ability to drive and use machines:

TRAMAZAC SR may affect the ability to drive and operate machinery. This applies particularly in conjunction with other psychotropic medicines including alcohol (see **INTERACTIONS**).

INTERACTIONS

Monoamine oxidase inhibitors (MAOIs): Because of its inhibitory effect on serotonin uptake, **TRAMAZAC SR** should not be used concomitantly with MAOIs or within 14 days after discontinuing such treatment (see **CONTRAINDICATIONS**). Life-threatening interactions with MAO-inhibitors affecting the central nervous system, breathing and circulation may occur during treatment with **TRAMAZAC SR**.

Serotonergic medicines, including lithium, tricyclic antidepressants and SSRIs: May lead to serotonergic syndrome (symptoms include confusion, restlessness, increased temperature, sweating) when used in combination with **TRAMAZAC SR**.

Central nervous system (CNS) depression-producing medications, including alcohol and anaesthetics: Caution is recommended because concurrent use may potentiate the CNS depressant effects. The duration of anaesthesia may be prolonged when **TRAMAZAC SR** is combined with barbiturates.

Carbamazepine: Serum concentrations of **TRAMAZAC SR** are reduced by carbamazepine, resulting in diminished analgesic activity of **TRAMAZAC SR**.

Warfarin: 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 **TRAMAZAC SR**.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol.

CYP2D6 inhibitors such as amitriptyline, fluoxetine, paroxetine and CYP3A4 inhibitors such as ketoconazole and erythromycin: May inhibit the metabolism of tramadol (*N*-demethylation) and the metabolism of the active *O*-demethylated metabolite.

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.

PREGNANCY AND LACTATION

Pregnancy

Safety in pregnancy and lactation has not been established. **TRAMAZAC SR** crosses the placental barrier. The repeated administration of **TRAMAZAC SR** during pregnancy may lead to dependence in the unborn baby. The neonate may experience withdrawal symptoms after birth.

Lactation

TRAMAZAC SR is excreted in breast milk.

DOSAGE AND DIRECTIONS FOR USE

The dosage should be adjusted to the intensity of pain and the individual's response to the analgesic action of **TRAMAZAC SR**. **TRAMAZAC SR** should not be used for the treatment of minor pain.

Adults and children over the age of 12 years:

Initial dose of 100 mg twice daily to be taken with a little liquid, independent of meal, preferably in the mornings and evenings.

If pain relief is not adequate, the dose may be increased to 150 mg or 200 mg twice daily.

The dosage intervals may be adjusted to individual requirements but should be at least 8 hours.

The lowest analgesic effective dose should generally be selected.

Daily doses of up to 400 mg tramadol are usually sufficient.

TRAMAZAC SR should not be used for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment with **TRAMAZAC 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.

Children under the age of 12 years:

TRAMAZAC SR is not recommended for children under the age of 12 years.

Elderly:

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended in the elderly.

Renal insufficiency / dialysis / hepatic insufficiency:

TRAMAZAC SR is not recommended in patients with severe renal and/or hepatic insufficiency. In moderate cases, prolongation of the dosage interval and possibly lower dosages, titrated upwards very carefully, should be considered.

SIDE EFFECTS

Immune system disorders:

Frequent: anaphylaxis, anaphylactoid reactions, bronchospasm

Less frequent: angioedema

Cardiac disorders:

Less frequent: bradycardia, tachycardia, cardiovascular collapse, palpitations, chest pain, myocardial infarction

Vascular disorders:

Less frequent: flushing, orthostatic hypotension, fainting, hypertension

Psychiatric disorders:

Frequent: depression

Less frequent: dependence, mood changes, confusion, hallucinations, sleep disorders, nightmares, changes in activity, decreased cognitive and sensory perception

Nervous system disorders:

Frequent: fatigue, agitation, anxiety, nervousness, sedation, drowsiness, dizziness, vertigo, muzziness, flushing, headache

Less frequent: hypaesthesia, paraesthesia, amnesia, seizures (see **WARNINGS AND SPECIAL PRECAUTIONS**), syncope, restlessness, abnormal gait, epileptic fits, a change in appetite, abnormal sensations, trembling, tremors

Gastrointestinal disorders:

Frequent: nausea, vomiting, dry mouth, dyspepsia, constipation, diarrhoea, anorexia, abdominal pain

Less frequent: urge to vomit, appendicitis, bloating, cholecystitis, cholelithiasis, pancreatitis

Hepato-biliary disorders:

Frequency unknown: increase in liver enzymes

Eye disorders:

Less frequent: miosis, blurred vision

Skin and subcutaneous tissue disorders:

Frequent: increased sweating, pruritus, skin rashes

Less frequent: toxic epidermal necrolysis, Stevens-Johnson syndrome, urticaria, vesicles, cellulitis, dermatitis

Musculoskeletal, connective tissue and bone disorders:

Less frequent: muscle weakness, arthralgia, myalgia, joint stiffness or swelling, back pain

Renal and urinary disorders:

Less frequent: urinary retention, urinary frequency, haematuria, dysuria

Respiratory disorders:

Less frequent: bronchospasm, nasal congestion, rhinorrhoea

Frequency unknown: slow breathing, dyspnoea, worsening of asthma, bronchitis

General disorders:

Frequent: asthenia, influenza-like illness

Less frequent: hypothermia (rigors).

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

Large doses produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur, especially in infants and children. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure.

Symptoms of overdose:

Pinpoint pupils, slow heartbeat, slow or troubled breathing, hypotension, weakness, seizures, cold, clammy skin, coma, dizziness.

Treatment of overdose:

Intensive supportive measures to correct respiratory failure and shock such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Treatment of restlessness is symptomatic and supportive.

Activated charcoal may be given by mouth within 1 hour in conscious patients if a substantial overdose has been ingested. It should be considered for all patients if a substantial amount of a sustained release preparation has been ingested. Gastric lavage has been used.

Naloxone should be used to reverse some, but not all, symptoms caused by overdosage with **TRAMAZAC SR**. Administration of naloxone should be done with caution because it may precipitate seizures.

Diazepam has been found to be effective in treating convulsions caused by **TRAMAZAC SR** toxicity.

Haemodialysis is not recommended in overdose, since it removes less than 7 % of the administered dose of **TRAMAZAC SR** in a 4-hour dialysis period.

IDENTIFICATION

TRAMAZAC SR 100: White to off-white, round shaped, biconvex, film coated tablets, debossed with “100” on one side and plain on the other side.

TRAMAZAC SR 150: Pale orange, round shaped, biconvex, film coated tablets, debossed with “150” on one side and plain on the other side.

TRAMAZAC SR 200: Slightly brownish orange, round shaped, biconvex, film coated tablets, debossed with “200” on one side and plain on the other side.

PRESENTATION

White opaque PVC/PVDC/aluminium blister strips containing 10 tablets per blister strip. 10, 30, 60 or 100 tablets will be packed into a cardboard box.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TRAMAZAC SR 100: 44/2.9/0496

TRAMAZAC SR 150: 44/2.9/0497

TRAMAZAC SR 200: 44/2.9/0498

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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