SCHEDULING STATUS: **S5**

PROPRIETARY NAMES AND DOSAGE FORMS:

TRAMAHEXAL CAPSULES

TRAMAHEXAL 100 mg/2 mℓ (solution for injection)

TRAMAHEXAL SR 100 (slow release tablets)

TRAMAHEXAL SR 150 (slow release tablets)

TRAMAHEXAL SR 200 (slow release tablets)

COMPOSITION:

Each TramaHexal Capsule contains 50 mg tramadol hydrochloride.

Each TramaHexal 100 mg/2 mℓ ampoule contains 100 mg tramadol hydrochloride.

Each TramaHexal SR 100 slow release tablet contains 100 mg tramadol hydrochloride.

Each TramaHexal SR 150 slow release tablet contains 150 mg tramadol hydrochloride.

Each TramaHexal SR 200 slow release tablet contains 200 mg tramadol hydrochloride.

Inactive ingredients:

TramaHexal Capsule:

Calcium hydrogen phosphate dihydrate, gelatin, indigotin (E 132), magnesium stearate, sodium starch glycollate, titanium dioxide (E 171) and yellow ferric oxide (E 172).

TramaHexal 100 mg/2 mℓ:

Sodium acetate trihydrate and water for injection.

TramaHexal SR 100, 150 and 200:

Calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, green varnish, hydrogenated castor oil, lactose monohydrate, magnesium stearate, maize starch, methyl hydroxypropyl-cellulose, microcrystalline cellulose, polyvidone and sodium starch glycolate.

Each TramaHexal capsule is sugar free.

Each TramaHexal SR 100 slow release tablet contains sugar (Lactose monohydrate 59,00 mg).

Each TramaHexal SR 150 slow release tablet contains sugar (Lactose monohydrate 88,50 mg).

Each TramaHexal SR 200 slow release tablet contains sugar (Lactose monohydrate 118,00 mg).

PHARMACOLOGICAL CLASSIFICATION:

A.2.9 Other analgesics

PHARMACOLOGICAL ACTION:

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 (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 enhancement of serotonin release.

Tramadol hydrochloride does not promote histamine release.

Pharmacokinetics:

Tramadol hydrochloride is readily absorbed following oral administration. 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.

The bioavailability of tramadol hydrochloride after intramuscular injection or intravenous administration is the same; the mean peak serum concentration is achieved after 45 minutes. Tramadol hydrochloride is primarily metabolised in the liver (90 %) with one of its metabolites, mono-O-desmethyltramadol (M1), being 2 to 4 times as potent as the parent compound.

Tramadol hydrochloride has a linear pharmacokinetic profile within the therapeutic dosage range. Tramadol hydrochloride and its metabolites are excreted mainly 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 barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

INDICATIONS:

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

CONTRAINDICATIONS:

- Hypersensitivity to tramadol hydrochloride or opioids.
- Acute intoxication with alcohol, hypnotics, analgesic 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.

WARNINGS AND SPECIAL PRECAUTIONS:

Avoid the use of TRAMAHEXAL 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 TRAMAHEXAL. TRAMAHEXAL does not suppress morphine withdrawal symptoms.

Use with caution in patients with a history of epilepsy or those susceptible to seizures (e.g. patients taking neuroleptics and other drugs that reduce the seizure threshold).
Use with caution in patients with renal or hepatic impairment and avoid if severe.

The administration of TRAMAHEXAL concurrently with other central nervous system medicines is likely to intensify and prolong CNS effects (see “INTERACTIONS”). Patients should be warned not to operate machinery or drive a car while using TRAMAHEXAL.
The possibility of respiratory depression cannot be excluded if the recommended dose is exceeded or other centrally depressant medicines are given concomitantly.
TRAMAHEXAL should not be used for the treatment of minor pain.

Lactose intolerance:
TRAMAHEXAL SR 100, 150 and 200 contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TRAMAHEXAL SR 100, 150 and 200.
TRAMAHEXAL SR 100, 150 and 200 contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

- Monoamine oxidase inhibitors (MAOIs): Because of its inhibitory effect on serotonin uptake, TRAMAHEXAL should not be used concomitantly with MAOIs or within 14 days after discontinuing such treatment (see “CONTRAINDICATIONS”).
- 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 TRAMAHEXAL is combined with barbiturates.

- Carbamazepine: Serum concentrations of TRAMAHEXAL are reduced by carbamazepine, resulting in diminished analgesic activity of TRAMAHEXAL. Inhibitors of CYP3A4 such as ketoconazole and erythromycin may inhibit the metabolism of TRAMAHEXAL.
- Incompatibilities: TRAMAHEXAL solution for injection is incompatible with the following injection solutions if mixed in the same syringe: Diclofenac, indomethacin, phenylbutazone, diazepam, flunitrazepam, midazolam, and glyceryl trinitrate.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see “CONTRAINDICATIONS”).

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 TRAMAHEXAL.

TRAMAHEXAL should not be used for the treatment of minor pain.

Adults and children over the age of 14 years:

Oral administration:

Initial dose of 50 mg, followed by 100 mg twice daily.

The dose may be increased to 150 mg or 200 mg twice daily.

Parenteral administration:

IV: 1 ampoule (100 mg – injected slowly or diluted in solution for infusion and infused).

IM: 1 ampoule (100 mg).

SC: 1 ampoule (100 mg).

Intravenous injection must be given slowly over 2 to 3 minutes.

A total daily dose of more than 400 mg per day must not be exceeded.

For post-operative 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 to 6 hourly up to a total daily dose of 600 mg. For less severe pain administer 50 mg or 100 mg 4 to 6 hourly.

Elderly:

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

Renal impairment:

The elimination of TRAMAHEXAL may be prolonged. The usual initial dose should be used, but for patients with creatinine clearance < 30 mℓ/min, the dosage interval should be increased to 12 hours.

Hepatic impairment:

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

Duration of treatment:

Under no circumstances should TRAMAHEXAL solution for injection be given for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment with TRAMAHEXAL solution for injection, evaluation should be carried out initially and at regular intervals to assess efficacy, adverse events, and the need for further treatment.

SIDE EFFECTS:

Cardiovascular system:

Flushing, syncope, bradycardia, tachycardia, postural hypotension and cardiovascular collapse have been reported.

Neurological:

- Dizziness, confusion, hallucinations and headache are frequently reported side effects.
- Other reported side effects are fatigue, sedation, drowsiness, seizures (see “WARNINGS AND SPECIAL PRECAUTIONS”), amnesia, parasthesia, syncope.

Gastrointestinal:

- Nausea, vomiting, dry mouth, dyspepsia, constipation, diarrhoea, anorexia and abdominal pain are frequently reported side effects.

Kidney / genitourinary:

- Urinary retention and urinary frequency have been reported.

Liver:

- Increase in liver enzymes has been reported.

Ocular:

- Blurred vision has been reported.

Skin:

- Sweating, skin rashes, urticaria, vesicles and pruritus have been reported.

Other:

- Angioedema, bronchospasm, anaphylaxis, and anaphylactoid reactions have been reported. These reactions may occur after the first dose.
- Other reported side effects include Toxic Epidermal Necrolysis and Steven-Johnson Syndrome.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose:

(See “SIDE EFFECTS”).

Symptoms of overdosage are typical of opioids, and include pinpoint pupils, slow heartbeat, slow or troubled breathing, weakness, seizures, cold, clammy skin.

Treatment of overdose:

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Treatment of restlessness is symptomatic and supportive.

Naloxone should be used to reverse some, but not all, symptoms caused by overdosage with TRAMAHEXAL.

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 TRAMAHEXAL toxicity.

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

IDENTIFICATION:

TramaHexal Capsules: Snap-fit, green cap and yellow body hard gelatine capsules (size 3), containing a white to off-white odourless powder.

TramaHexal 100 mg/2 mℓ: A clear colourless solution, free from visible particles, packed in a sterile colourless glass ampoule of 2 mℓ capacity.

TramaHexal SR 100**:** Flat, round bi-layer tablets with facet, initial layer white, slow release layer green with one sided identification mark TR 100R

TramaHexal SR 150: Flat, round bi-layer tablets with facet, initial layer white, slow release layer green with one sided identification mark TR 150R

TramaHexal SR 200: Flat, round bi-layer tablets with facet, initial layer white, slow release layer green with one sided identification mark TR 200R

PRESENTATIONS:

TramaHexal Capsules: White, opaque securitainers containing 20 or 100 capsules.

TramaHexal 100 mg/2 mℓ: Sterile colourless glass ampoules of 2 mℓ capacity. 5 ampoules per pack.

TramaHexal SR 100: Carton containing 10, 30, 60 or 100 tablets in Polypropylene / Aluminium blister strips of 10's.

TramaHexal SR 150: Carton containing 10, 30, 60 or 100 tablets in Polypropylene / Aluminium blister strips of 10's.

TramaHexal SR 200: Carton containing 10, 30, 60 or 100 tablets in Polypropylene / Aluminium blister strips of 10's.

STORAGE INSTRUCTIONS:

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

Do not remove the blisters from the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

TramaHexal Capsules: 32/2.9/0652

TramaHexal 100 mg/2 mℓ: 36/2.9/0397

TramaHexal SR 100: 38/2.9/0092

TramaHexal SR 150: 38/2.9/0093

TramaHexal SR 200: 38/2.9/0094

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

DATE OF PUBLICATION:

Date of registration: 17 February 2006

Date of the most recent approval of the professional information: 12 February 2015

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	TramaHexal Capsules (20 capsules)	S1A	BOT1302472A
	TramaHexal Capsules (100 capsules)	S1A	BOT1302472B
	TramaHexal SR 100 (10 tablets)	S1A	BOT1302467A
	TramaHexal SR 100 (30 tablets)	S1A	BOT1302467B
	TramaHexal SR 100 (60 tablets)	S1A	BOT1302467C
	TramaHexal SR 100 (100 tablets)	S1A	BOT1302467D
	TramaHexal SR 150 (10 tablets)	S1A	BOT1302471A
	TramaHexal SR 150 (30 tablets)	S1A	BOT1302471B
	TramaHexal SR 150 (60 tablets)	S1A	BOT1302471C
	TramaHexal SR 150 (100 tablets)	S1A	BOT1302471D
Namibia	TramaHexal 100 mg/2 mℓ	NS3	05/2.9/0507

TramaHexal Capsules	NS3	04/2.9/1357
TramaHexal SR 100	NS3	12/2.9/0089
TramaHexal SR 150	NS3	12/2.9/0090
TramaHexal SR 200	NS3	12/2.9/0091

ATC code: N02AX02 – Other opioids

Name and address of manufacturer:

Salutas Pharma GmbH
Otto-von Guericke-Allee 1
D-39179 Barleben
Germany

[1]Company Reg. No.: 1990/001979/07