PACKAGE INSERT

SCHEDULING STATUS

Schedule 5

PROPRIETARY NAME AND DOSAGE FORM

TRAMAL ® Capsules

COMPOSITION

Each capsule contains tramadol hydrochloride 50 mg.

Capsule powder excipients are as follows: colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

The capsule shell comprises of: gelatine, sodium lauryl sulphate, titanium dioxide (E171) and yellow iron oxide (E172).

PHARMACOLOGICAL CLASSIFICATION

A.2.9.Other analgesics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Tramadol hydrochloride is a centrally acting analgesic with binding to specific opioid receptors. It is a non-selective, agonist at mu (μ), delta (δ) and kappa (k) opioid receptors with a higher affinity for the μ receptor. Other mechanisms, which contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline

as well as the enhancement of serotonin release. The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably. Patients devoid of CYP2D6 may need higher doses of tramadol, to achieve adequate analgesia.

Pharmacokinetic properties

After oral administration of TRAMAL capsules, tramadol hydrochloride is absorbed with an absorption half-life ($t_{½\ ka}$) of 0,38 ± 0,18 hours. The mean systemic bioavailability is 68 %, independent of food intake.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. 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 ($t_{½\beta}$) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean $t_{½\beta}$ of tramadol was 13,3 ± 4,9 h, $t_{½,\ \beta}$/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.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

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

INDICATIONS

Management of moderate to moderately severe pain.

CONTRAINDICATIONS

- Known hypersensitivity to tramadol hydrochloride or opioids or any of the ingredients of TRAMAL.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- TRAMAL capsules should not be given to patients with epilepsy.

TRAMAL capsules must not be used for narcotic withdrawal treatment.

TRAMAL capsules should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.

TRAMAL capsules should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

TRAMAL capsules should not be used in pregnant and breastfeeding women (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS

TRAMAL capsules may only be taken with special care in opioid dependence.

TRAMAL capsules are not suitable for children under the age of 12 years.

TRAMAL capsules should be used with care in patients with increased reactivity to opioids.

Respiratory depression may develop if the recommended dosages are exceeded or other centrally depressant medicines are given concomitantly.

TRAMAL capsules should not be used in the treatment of minor pain.

TRAMAL capsules should be used with caution in patients with impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. (See DOSAGE AND DIRECTIONS FOR USE).

Seizures

Seizures have been reported in patients receiving TRAMAL capsules 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, MAO-inhibitors and neuroleptics.

Drug Abuse and Dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop. TRAMAL capsules have been associated with craving drug-seeking behaviour and tolerance development. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms. Other symptoms that have been seen with TRAMAL capsules discontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation and paranoia).

TRAMAL capsules should not be used in opioid-dependent patients. TRAMAL capsules can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with TRAMAL capsules are not recommended.

CYP2D6 Ultra-rapid metabolism of tramadol:

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Hyponatraemia:

Hyponatraemia has been reported with the use of TRAMAL, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of TRAMAL and appropriate treatment (e.g. fluid restriction). During TRAMAL treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Effects on ability to drive or operate machinery

TRAMAL capsules may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.

INTERACTIONS

TRAMAL capsules should not be combined with MAO inhibitors within 14 days of withdrawal of MAO inhibitors (see CONTRAINDICATIONS).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions of the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with TRAMAL capsules.

Concomitant administration of TRAMAL capsules with other centrally depressant medicines including alcohol may potentiate the CNS effects (see CONTRAINDICATIONS).

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

TRAMAL capsules can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetra-hydrocannabinol) to cause convulsions.

Concomitant therapeutic use of TRAMAL capsules and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see CONTRAINDICATIONS), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. The 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 ^{o}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.

Caution should be exercised during concomitant treatment with TRAMAL capsules and warfarin–like medicines due to reports of increased International Normalised Ratio (INR) with major bleeding and ecchymoses in some patients.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

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 Pharmacokinetic properties).

The antiemetic 5-HT3 antagonist ondansetron increases the requirement of TRAMAL capsules in patients with postoperative pain. TRAMAL capsules may decrease the antiemetic efficacy of ondansetron.

PREGNANCY AND LACTATION

Pregnancy

Safety during pregnancy and lactation has not been established. Therefore, TRAMAL capsules should not be used in pregnant women. TRAMAL crosses the placenta.

Animal studies with TRAMAL revealed effects on organ development, ossification and neonatal mortality.

The administration of TRAMAL capsules during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see CONTRAINDICATIONS).

Breastfeeding

TRAMAL passes into breastmilk. Mothers on TRAMAL capsules should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

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

In principle, the lowest pain-relieving dose should be selected. In general, a total oral daily dose of 400 mg of Tramadol (equivalent to 8 TRAMAL capsules) should not be exceeded.

The recommended dosages are guidelines.

TRAMAL capsules should be taken as follows:

Adults and children over 12 years

Moderate pain:

Initial dose of 50 mg of Tramadol (1 TRAMAL capsule), followed by 50 mg or 100 mg 4-6 hourly.

Severe pain:

Initial dose of 100 mg followed by 50 mg or 100 mg 4-6 hourly.

Capsules are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Paediatric population

On account of the high dosage strength, TRAMAL capsules are not intended for children below the age of 12 years.

Elderly patients

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

Patients with renal insufficiency/dialysis

In patients with renal 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 insufficiency TRAMAL capsules are not recommended.

Patients with hepatic impairment

In patients with 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 hepatic insufficiency TRAMAL capsules are not recommended.

Duration of treatment

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

SIDE EFFECTS

TRAMAL capsules have side effects. These are classified as follows:

- very common (≥1/10)
- common (≥1/100, <1/10)
- uncommon (≥1/1000, <1/100)
- rare (≥1/10 000, <1/1000)
- very rare (<1/10 000, including isolated reports)

The most common side effects during treatment with TRAMAL capsules are nausea and dizziness, which occur more frequently than 1 in 10 patients.

Immune system disorders

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.

Metabolism and nutrition disorders

Rare: changes in appetite.

Psychiatric disorders

Rare: Hallucinations, confusional states, sleep disturbances, delirium, anxiety and nightmares. Changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensorial capacity (such as decision behaviour, perception disorders).

Nervous system disorders

Very common: dizziness

Common: headaches, somnolence

Rare: speech disorders, paraesthesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope.

Eye disorders

Rare: miosis, mydriasis, blurred vision.

Cardiac disorders

Uncommon: dysrhythmias, palpitation, tachycardia.

Rare: bradycardia.

Vascular disorders

Uncommon: postural hypotension, cardiovascular collapse.

Rare: increase in blood pressure.

Respiratory, thoracic and mediastinal disorders

Rare: respiratory depression, dyspnoea, bronchospasm.

Gastrointestinal disorders

Very common: nausea

Common: vomiting, constipation, dry mouth.

Uncommon: retching, gastrointestinal discomfort.

Hepatobiliary disorders

Very rare: increase in transaminases (ALT and AST) is expected.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis

Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal, connective tissue and bone disorders

Rare: muscular weakness.

Renal and urinary disorders

Rare: micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions:

Common: fatigue.

Post-marketing experience

The following post-marketing experiences have been reported:

Nervous system complaints

Speech disorders.

Eye disorders

Mydriasis.

Skin and subcutaneous tissue disorders

Stevens Johnson Syndrome,

Toxic Epidermal Necrolysis.

Cases of hyponatraemia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatraemia.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

Symptoms

Following an overdose with TRAMAL capsules, 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, cardiovascular collapse, consciousness

disorders, coma, convulsions, respiratory depression and respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract, maintain respiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone). Convulsions should be treated with intravenous diazepam.

In cases of intoxication with oral formulations, gastrointestinal decontamination with activated charcoal is only recommended within 2 hours after TRAMAL capsules intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

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

IDENTIFICATION

Capsules: ObIong, hard gelatine capsule with snap-fit closure. Cap and body: pale – yellow opaque.

PRESENTATION

Blister packs of 20 and 100 capsules.

STORAGE INSTRUCTIONS

Store at or below 30 °C, in a cool dry place.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

S/2.9/289

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

JANSSEN PHARMACEUTICA (Pty.) Ltd.

(Reg No.: 1980/011122/07)

2 Medical Road,

Halfway House, Midrand, 1685

Tel: +27 (11) 518 7000

RA-JACZA-MedInfo@its.jnj.com

DATE OF PUBLICATION OF THE PACKAGE INSERT

- Date on the registration certificate: 17 May 1991
- Date of the last approved Package insert: 4 August 2017