SCHEDULING STATUS
Schedule 5

PROPRIETARY NAME AND DOSAGE FORM
TRAMAL® 100 Ampoules

COMPOSITION
Each ampoule contains tramadol hydrochloride 100 mg.
The other ingredients are: sodium acetate and water for injection.

PHARMACOLOGICAL CLASSIFICATION
A.2.9.Other analgesics

PHARMACOLOGICAL ACTION
Pharmacodynamics
Tramadol hydrochloride is a centrally acting analgesic with binding to specific opioid receptors. It is a non-selective, pure agonist at mu (\(\mu\)), delta (\(\delta\)) and kappa (\(k\)) opioid receptors with a higher affinity for the \(\mu\) 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.
**Pharmacokinetics**

After intramuscular injection of tramadol hydrochloride, the bioavailability is the same as after i.v. administration; the mean peak serum concentration is achieved after 45 minutes.

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 ($t_{1/2}$) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean $t_{1/2}$ of tramadol was $13.3 \pm 4.9$ h, $t_{1/2, M1}$ $18.5 \pm 9.4$ h, in patients with renal insufficiency (creatinine clearance $\leq 5$ ml / min) the values were $11.0 \pm 3.2$ h (tramadol) and $16.9 \pm 3.0$ h (M1) respectively.

**INDICATIONS**

Management of moderate to moderately severe pain.

**CONTRA-INDICATIONS**

TRAMAL is contra-indicated in known hypersensitivity to tramadol hydrochloride or any of the excipients, 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.

Further, TRAMAL 100 should not be given to patients with epilepsy not adequately controlled by treatment.

TRAMAL must not be used for narcotic withdrawal treatment.

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

**WARNINGS**

TRAMAL may only be taken with special care in opioid dependence, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory function and increased intracranial pressure.

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

The preparation should be used with care in patients with increased reactivity to opioids.

**Seizures**

Seizures have been reported in patients receiving TRAMAL 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, or selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics. Patients with epilepsy or those susceptible to seizures should only be treated if there are compelling circumstances. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with TRAMAL.

**Drug Abuse and Dependence**

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop. TRAMAL has been associated with craving drug-seeking behaviour and tolerance development. Cases of abuse and dependence on TRAMAL have been reported. TRAMAL should not be used in opioid-dependent patients. TRAMAL 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 is not recommended.
Effects on ability to drive or operate machinery

TRAMAL 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 psychotrophic medicines including alcohol.

INTERACTIONS

TRAMAL should not be combined with MAO inhibitors (see section CONTRA-INDICATIONS).

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 TRAMAL.

Concomitant administration of TRAMAL with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. 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 TRAMAL is not advisable, because the analgesic effect of a pure agonist like TRAMAL may be theoretically reduced in such circumstances.

TRAMAL can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, anti-psychotics and other seizure threshold-lowering medicinal products to cause convulsions.
There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of TRAMAL in combination with other serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Caution should be exercised during concomitant treatment with TRAMAL and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

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 SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

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

TRAMAL solution for injection has proven to be incompatible (cannot be mixed) with solutions for injection of

- diazepam
- diclofenac
- flunitrazepam
- glyceryl trinitrate
- indomethacin
- midazolam
- phenylbutazone
PREGNANCY AND LACTATION

Pregnancy

Safety during pregnancy and lactation has not been established. Therefore TRAMAL 100 should not be used in pregnant women. TRAMAL crosses the placenta. Animal studies with TRAMAL revealed at very high doses effects on organ development, ossification and neonatal mortality.

TRAMAL 100 (administered before or during birth) does not affect uterine contractility. In neonates it may induce changes in the respiratory rate usually not clinically relevant.

The administration of TRAMAL 100 ampoules during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth.

Breast-feeding

About 0.1 % of the dose taken by the mother, passes into the milk. Therefore, TRAMAL 100 is not recommended during breast-feeding. After a single administration of TRAMAL 100 it is not usually necessary to interrupt breast-feeding.

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. The recommended dosages are guidelines.

Unless otherwise prescribed, TRAMAL 100 ampoules should be administered as follows:

Adults and children over 12 years:

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)

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 600 mg. For less severe pain administer 50 mg or 100 mg 4 – 6 hourly.

**Elderly**
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 TRAMAL 100 ampoules are not recommended.

**Duration of treatment**
Under no circumstances should TRAMAL 100 be given for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment with TRAMAL 100, 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.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**
TRAMAL 100 ampoules may 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 100 ampoules are nausea and dizziness, which occur more frequently than 1 in 10 patients.

Heart and circulation problems

Uncommon: Effects on the heart and blood circulation (pounding of the heart, fast heart-beat, head rush or cardiovascular collapse).

These side-effects may appear particularly on intravenous administration, under physical strain or when the patient is in an upright position (postural hypotension).

Rare: Slow heart-beat, increase in blood pressure.

Nervous system complaints

Very common: Dizziness

Common: Headaches, somnolence

Rare: Changes in appetite, abnormal sensations (e.g. itching, tingling, numbness), trembling, slow breathing, epileptic seizures; involuntary muscle contractions, abnormal coordination, fainting.

If the recommended doses are exceeded, or if other medicines are taken which depress brain function, slow breathing may occur.

Epileptic fits occurred mainly after taking high doses of TRAMAL or when medicines that may cause fits themselves or lower the fit threshold were taken at the same time.

Psychological side-effects

Rare: Hallucinations, confusion, sleep disorders, anxiety and nightmares.

Psychological complaints may appear after treatment with TRAMAL 100 ampoules. Their intensity and nature may vary (according to the patient’s personality and length of therapy). These may appear as a change in mood (mostly high spirits, occasionally irritated mood), changes in activity (usually suppression, occasionally increase) and decrease cognitive and sensory
perception (changes in senses and recognition, which may lead to errors in judgment).

Dependence may occur.

**Visual disorders**

Rare: Blurred vision

**Difficulty in breathing**

Rare: Shortness of breath

Worsening of asthma has also been reported, but it has not been established whether it was caused by the active substance tramadol.

**Stomach and bowel problems**

Very common: Nausea

Common: Vomiting, constipation, dry mouth.

Uncommon: Urge to vomit, stomach trouble (e.g. feeling of pressure in stomach, bloating), diarrhoea.

**Skin and skin appendages**

Common: Sweating.

Uncommon: Skin reactions (e.g. itching, rash).

**Bones and muscles**

Rare: Weak muscles.

**Liver and bile complaints**

Very rare: Increase in liver enzyme values.

**Difficulties in passing water**

Rare: Difficulties in passing water, painful urination or less urine than normal.
General condition

Common: Fatigue

Rare: Allergic reactions (e.g. difficulty in breathing, bronchospasm, wheezing, rapid swelling of the dermis, subcutaneous tissue, mucosa, submucosal tissues) and anaphylaxis (sudden systemic allergic reaction).

Symptoms of withdrawal reactions may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastro-intestinal symptoms.

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

Dependence may occur. (see Warnings). After discontinuation of TRAMAL 100 ampoules signs of withdrawal may appear.

Post-marketing experience

The following post-marketing experiences have been reported:

Nervous system complaints
Speech disorders
Visual disorders
Mydriasis

Special Precautions:

The possibility of respiratory depression cannot be excluded if the recommended dosages are exceeded or other centrally depressant medicines are given concomitantly.

TRAMAL should not be used in the treatment of minor pain.
Rapid intravenous administration may be associated with higher incidence of adverse events and should therefore be avoided. TRAMAL 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)

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT**

**Symptoms**
In principle, on intoxication with TRAMAL, 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 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.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone). In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In cases of intoxication with oral formulations, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol hydrochloride intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

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

**IDENTIFICATION**
Ampoules: Clear, colourless solution in clear, type I glass ampoules.

PRESENTATION

Packs of 5 ampoules, each containing 2 ml.

STORAGE INSTRUCTIONS

Store in a cool (below 25 °C), dry place.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

S/2.9/290

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