**SCHEDULING STATUS**

S5

## 1 NAME OF THE MEDICINAL PRODUCT

TRAMADOL UNIMED (50 mg capsules)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TRAMADOL UNIMED capsule contains 50 mg tramadol hydrochloride.

Sugar free

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsules

Green/yellow size 4 hard gelatine capsules filled with white to off-white powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Management of moderate to severe pain.

### 4.2 Posology and method of administration

**Posology**

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

The lowest effective dose for analgesia should generally be selected.

The total daily dose of 400 mg of TRAMADOL UNIMED (equivalent of 8 capsules) should not be exceeded.

The recommended dosages below are only guidelines.

TRAMADOL UNIMED should be taken as follows:

Adults and children 12 years and older

*Moderate pain:*

An initial dose of 50 mg of Tramadol (1 TRAMADOL UNIMED capsule), followed by 50 mg or 100 mg at 4 - 6 hourly.

*Severe Pain:*

An initial dose of 100 mg followed by 50 mg or 100 mg at 4 – 6 hourly.

**Special Populations**

*Elderly patients*

In elderly patients older than 75 years elimination may be prolonged, therefore, a downward adjustment of the dosage and /or the extension of the interval between doses are recommended.

*Renal insufficiency/dialysis and 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/hepatic insufficiency TRAMADOL UNIMED capsules are not recommended.

*Paediatric population*

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

**Method of administration**

For oral administration

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

*Duration of administration*

Under no circumstances should TRAMADOL UNIMED 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 TRAMADOL UNIMED capsules is necessary.

## 4.3 Contraindications

TRAMADOL UNIMED is contraindicated:

- in known hypersensitivity to tramadol hydrochloride or any of the excipients in TRAMADOL UNIMED (see section 6.1)
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicines,
- in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days (see section 4.5),
- in patients with epilepsy,
- for use in narcotic withdrawal treatment.
- in patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.
- in patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
- in pregnancy and lactation (see section 4.6).

## 4.4 Special warnings and precautions for use

TRAMADOL UNIMED are not suitable for children under the age of 12 years

It should not be used in the treatment of minor pain

TRAMADOL UNIMED may only be used with special caution in:

- opioid-dependent patients.
- patients sensitive to opiates.

Respiratory depression may develop if other centrally depressant medicines are given concomitantly. It may result in sedation, respiratory depression, coma and death. Because of these risks concomitant prescribing with these sedating medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe TRAMADOL UNIMED concomitantly with sedating medicinal products, the lowest effective dose of TRAMADOL UNIMED should be used, and the duration of the concomitant treatment should be as short as possible.
The patients should be followed 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 (see section 4.5).

Care should be taken if the recommended dosage of TRAMADOL UNIMED is significantly exceeded (see section 4.9) as respiratory depression may develop.

TRAMADOL UNIMED should be used with caution in patients with impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

**Seizures**

Seizures have been reported in patients receiving TRAMADOL UNIMED at the recommended dose levels. The risk may be increased when doses exceed the recommended daily dose limit (400 mg). In addition, TRAMADOL UNIMED may increase the seizure risk in patients taking tricyclic antidepressants or other tricyclic compounds e.g. promethazine, selective serotonin re- uptake inhibitors, MAO-inhibitors and neuroleptics that lowers the seizure threshold (see section 4.5).
Patients with epilepsy or those susceptible to seizures should be only treated with TRAMADOL UNIMED if there are compelling circumstances.

**Sleep-related breathing disorders**

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

**Drug abuse and dependence**

TRAMADOL UNIMED has a dependence potential and tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop, especially after long-term use. TRAMADOL UNIMED have been associated with craving drug-seeking behaviour and tolerance development.

It should not be used in opioid dependant patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

It can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids.

Treatment with TRAMADOL UNIMED is not recommended in patients with a tendency to drug abuse, a history of drug dependence, or who are chronically using opioids.

When a patient no longer requires therapy with TRAMADOL UNIMED, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Symptoms of withdrawal, 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 TRAMADOL UNIMED capsules discontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesia's, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation and paranoia).

**CYP2D6 metabolism**

TRAMADOL UNIMED 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.

However, if the patient is a CYP2D6 ultra-rapid metaboliser, he/she may convert tramadol, as contained in TRAMADOL UNIMED 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 which may be life threatening and very rarely fatal.

Alternative medication, dose reduction and/or increased monitoring for signs of TRAMADOL UNIMED overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

**Hyponatraemia**

Cases of hyponatraemia have been reported in patients taking TRAMADOL UNIMED, usually in patients with predisposing risk factors, such as those using concomitant medicines 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 TRAMADOL UNIMED and appropriate treatment (e.g. fluid restriction). During TRAMADOL UNIMED treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

**Mental health disorders**

TRAMADOL UNIMED is associated with an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders including, but not limited to major depression, anxiety and alcohol and drug abuse.

**Paediatric population**

TRAMADOL UNIMED are not suitable for children younger than 12 years of age (see section 4.2).

**Important information about some of the ingredients of TRAMADOL UNIMED**

TRAMADOL UNIMED contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially “sodium-free”.

## 4.5 Interaction with other medicinal products and other forms of interaction

TRAMADOL UNIMED should not be combined with MAO inhibitors within 14 days of withdrawal of MAO inhibitors (see section 4.3).

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 TRAMADOL UNIMED.

Concomitant administration of TRAMADOL UNIMED with other centrally depressant medicines including alcohol may potentiate the CNS effects (see section 4.8).

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

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

TRAMADOL UNIMED can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold- lowering medicine (such as bupropion, mirtazapine, tehrahydro-cannabinol) to cause convulsions.

Concomitant therapeutic use of TRAMADOL UNIMED and serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic anti-depressants and mirtazapine may cause serotonin toxicity.

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 °C and inducible 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 TRAMADOL UNIMED and coumarin derivatives (e.g. warfarin) due to reports of increased 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 section 4.8).

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

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

The safety of TRAMADOL UNIMED during pregnancy has not been established and therefore it should not be used in pregnant women.

Animal studies with TRAMADOL UNIMED revealed effects on organ development, ossification and neonatal mortality. It crosses the placenta.

Administration during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3).

**Breastfeeding**

TRAMADOL UNIMED is excreted in breastmilk, and should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with TRAMADOL UNIMED.

**Fertility**

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

### 4.7 Effects on ability to drive and use machines

TRAMADOL UNIMED may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly if used in conjunction with other psychotropic substances, including alcohol.

### 4.8 Undesirable effects

#### a. Summary of the safety profile

TRAMADOL UNIMED capsules have side effects.

The most frequently reported adverse reactions are nausea and dizziness, both occurring more frequently than 1 in 10 patients.

Cardiovascular regulation (postural hypotension or cardiovascular collapse). may occur especially in patients who are physically stressed

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

Convulsions occurred mainly after administration of high doses of TRAMADOL UNIMED or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.4 and 4.5).

#### b. Tabulated summary of the adverse effects

Frequencies have been evaluated according to the following convention:

Frequent = more frequent, very common and common

Less frequent = single reports/isolated reports, uncommon, rare and very rare

Frequency not known (no frequency data available).

| **MedDRA System Organ Classification (SOC) according to the sequence:** | **Adverse Reaction** | **Frequency per patient** |
|---|---|---|
| Immune system disorders (see section 4.4) | allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis | less frequent |
| Psychiatric disorders | hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares, changes in mood (euphoria, dysphoria), decreased activity restlessness and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). | less frequent |
| Nervous system disorders | dizziness<br>headache, somnolence<br>paraesthesia, tremor, epileptiform convulsions involuntary muscle contractions, abnormal coordination, syncope, speech disorders. | frequent<br>frequent<br>less frequent |
| Cardiac disorders: | palpitation, tachycardia, dysrhythmias<br>bradycardia | less frequent<br>less frequent |
| Vascular disorders | postural hypotension, cardiovascular collapse<br>increase in blood pressure | less frequent<br>less frequent |
| Respiratory, thoracic and mediastinal disorders | respiratory depression, dyspnoea, bronchospasm | less frequent |

| **MedDRA System Organ Classification (SOC) according to the sequence:** | **Adverse Reaction** | **Frequency per patient** |
|---|---|---|
| Metabolism and nutrition disorders | changes in appetite<br>hypoglycaemia | less frequent<br>frequency not known |
| Gastrointestinal disorders | nausea<br>vomiting, constipation, dry mouth<br>retching; gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea | frequent<br>frequent<br>less frequent |
| Musculoskeletal and connective tissue disorders | muscular weakness | less frequent |
| Hepatobiliary disorders | increase in liver enzyme values | less frequent |
| Renal and urinary disorders | micturition disorders (dysuria and urinary retention) | less frequent |
| Eye disorders | miosis, mydriasis, blurred vision | Less frequent |
| Skin and subcutaneous Tissue disorders | hyperhidrosis<br>dermal reactions (e.g. pruritus, rash, urticaria) | less frequent<br>less frequent |
| General disorders | fatigue | frequent |
| Investigations | increase in blood pressure | less frequent |

**Post-marketing experience**

The following post-marketing experiences have been reported:

| **MedDRA System Organ Classification (SOC) according to the sequence:** | **Adverse Reaction** | **Frequency** |
|---|---|---|
| Nervous system | speech disorders | Not known |
| Gastrointestinal disorders | Increased risk of abdominal pain, including pancreatitis has been reported | Rare |
| Eye disorders | mydriasis | Not known |
| Skin and subcutaneous tissue disorders | Stevens Johnson Syndrome, Toxic epidermal necrolysis. | Not known |

Cases of hyponatraemia and/or SIADH have been reported in patients taking TRAMADOL UNIMED, concomitantly with medicines that may cause hyponatraemia.

**c. Description of selected adverse reactions**

Psychic adverse reactions may occur following administration of TRAMADOL UNIMED which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Drug dependence may occur.

Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, 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, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

**d. Other special populations**

Cases of hyponatraemia and/or SIADH have been reported in patients taking TRAMADOL UNIMED, usually in patients with predisposing risk factors, such as the elderly.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

*Symptoms*

Following an overdose with TRAMADOL UNIMED symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

*Treatment*

The general emergency measures apply. Keep the respiratory tract open, maintain respiration and circulation depending on the symptoms.

The antidote for respiratory depression is naloxone. Convulsions should be treated with diazepam given intravenously.

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

TRAMADOL UNIMED is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with TRAMADOL UNIMED with haemodialysis or haemofiltration alone is not suitable for detoxification.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Medicine Class: A.2.9 Other analgesics

Pharmacotherapeutic group: other opioids; ATC code: N02 AX02

*Mechanism of action*

Tramadol hydrochloride is a centrally acting opioid analgesic. 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 contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and 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 hydrochloride, to achieve adequate analgesia.

### 5.2 Pharmacokinetic properties

**Absorption**

More than 90 % of tramadol hydrochloride is absorbed after oral administration.

The mean systemic bioavailability is approximately 70 %, irrespective of the concomitant intake of food. Tramadol is mainly metabolised in the liver (90 %).
The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean $C_{max}$ of 280 to 208 mcg/L and $T_{max}$ of 1,6 to 2h.

**Distribution**

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breastmilk (0,1 % and 0,02 % respectively of the applied dose).
It has a high tissue affinity (V d,ß = 203 ± 40 l), and has a plasma protein binding of about 20 %.

**Elimination**

Elimination half-life t1/2, ß is approximately 5 - 7 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1,4.
Tramadol and its metabolites are almost completely excreted via the kidneys.

Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13,3 ± 4,9 h (tramadol) and 18,5 ± 9,4 h (O- desmethyltramadol), in an extreme case 22,3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3,2 h and 16,9 ± 3 h, in an extreme case 19,5 h and 43,2 h respectively.

**Biotransformation**

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4.
It's half-life $t_{1/2}$, ß (6 healthy volunteers) is 7,9 h (range 5,4 – 9,6 h) and is approximately that of tramadol.

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

**Linearity**

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule powder: colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

Capsule shell: gelatin, water, sodium lauryl sulphate, indigo carmine (E132), iron oxide yellow (E172), titanium dioxide (E171).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store at or below 25 °C.

### 6.5 Nature and contents of container

20 capsules in a printed cardboard carton (2 PVC/PVdC aluminium foil blister packs of 10 capsules each).

100 capsules in a printed cardboard carton (10 PVC/PVdC aluminium foil blister packs of 10 capsules each).

## 6.6 Special precautions for disposal and other handling

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

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## 8 REGISTRATION NUMBER

50/2.9/0401

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 January 2022

## 10 DATE OF REVISION OF THE TEXT

09 September 2024