

## Summary of Product Characteristics

### 1. Name of the medicinal product

Tramadol Denk 50

Active substance: tramadol hydrochloride

### 2. Qualitative and quantitative composition

1 effervescent tablet contains 50 mg tramadol hydrochloride.

Contains aspartame, lactose and sodium.

For a full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Effervescent tablets

Tramadol Denk 50 are white, round, flat effervescent tablets.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Moderately severe to severe pain

#### 4.2 Posology and method of administration

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.

Unless otherwise prescribed, Tramadol Denk 50 should be dosed as follows:

##### Adults and adolescents aged 12 years and older

For moderately severe pain, 1 Tramadol Denk 50 effervescent tablet (equivalent to 50 mg tramadol hydrochloride). If no pain relief occurs within 30 - 60 minutes, a second effervescent tablet can be taken.

If the demand is likely to be higher for severe pain, 2 Tramadol Denk 50 effervescent tablets (equivalent to 100 mg tramadol hydrochloride) are taken as a single dose.

Depending on the pain, the effect lasts for 4 - 8 hours. It is generally not necessary to exceed daily doses of 8 effervescent tablets (equivalent to 400 mg tramadol hydrochloride). However, even much higher doses may be required for tumour pain and severe postoperative pain. More suitable pharmaceutical forms may have to be selected.

### Children

Tramadol Denk 50 is not intended for use in children below 25 kg body weight and does not generally allow for individual dosing in children below 12 years of age. More suitable pharmaceutical forms should therefore be selected.

### Geriatric patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

### Renal insufficiency/dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

### *Note:*

The recommended dosages are guideline values. In general, the lowest analgesically effective dose should be selected. When treating chronic pain, fixed-schedule dosing should be preferred.

### **Method and duration of administration**

Prior to ingestion, the effervescent tablets are dissolved in a glass of water. They can be taken with or without a meal.

Tramadol Denk 50 should on no account be taken for longer than therapeutically absolutely necessary. If, depending on the nature and severity of the disease, longer-term analgesic treatment with Tramadol Denk 50 seems necessary, careful and regular checks should be made at short intervals (if necessary, by inserting breaks in treatment) to establish whether and to what extent there is still a medical need.

### **4.3 Contraindications**

Tramadol Denk 50 must not be used in the following cases:

- known hypersensitivity to tramadol or to any of the excipients;
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic agents;
- patients receiving MAO inhibitors or having used them within the last 14 days (see "Interaction with other medicinal products");
- epilepsy that cannot be adequately controlled by treatment.

Tramadol Denk 50 must not be used for drug substitution.

Tramadol Denk 50 is not intended for use in children below 25 kg body weight (see also "Posology and method of administration").

## **Warnings and precautions for use**

Tramadol Denk 50 may be used only after careful consideration of the benefit/risk ratio, together with appropriate precautions, in the following cases:

- opioid dependence,
- impaired consciousness of unclear origin, shock,
- disturbances of the respiratory centre and respiratory function,
- conditions with increased intracranial pressure in patients with head injuries or cerebral disease,
- impaired hepatic or renal function.

In patients sensitive to opiates, Tramadol Denk 50 should only be used with caution.

Seizures have been reported in patients taking tramadol at the recommended dosage. There may be an increased risk when administering dosages that exceed the recommended daily dose (400 mg). Upon concomitant administration of medicines that lower the seizure threshold, tramadol can increase the risk of seizures (see “Interaction with other medicinal products”). Patients with epilepsy or seizure susceptibility should be treated with tramadol only in compelling, exceptional cases.

Tramadol has a low potential for dependence. Tolerance, psychiatric and physical dependence may develop with prolonged use. In patients with a tendency for drug abuse or dependence, treatment with Tramadol Denk 50 should therefore be administered only over short periods and under very strict medical surveillance.

Tramadol Denk 50 is not suitable as a drug substitute in opiate dependence. Although tramadol is an opiate agonist, it is unable to suppress morphine withdrawal symptoms.

Tramadol Denk 50 contains aspartame as a source of phenylalanine and may be harmful for patients with phenylketonuria.

### Further precautionary measures

Patients suffering from the rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take Tramadol Denk 50.

One effervescent tablet contains 9.3 mmol (214 mg) sodium. To be considered by patients on a sodium-controlled (low sodium/low salt) diet.

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

Life-threatening interactions, affecting the central nervous system and respiratory/circulatory function, have been seen in patients pre-treated with MAO inhibitors within 14 days prior to administration of the opioid pethidine. These same interactions with MAO inhibitors cannot be excluded with Tramadol Denk 50.

Mutual potentiation of the central effects is likely when Tramadol Denk 50 is co-administered with substances that also act on the central nervous system, including alcohol.

Based on the pharmacokinetic results available, no clinically relevant interactions are anticipated with cimetidine (an enzyme inhibitor) given concomitantly or previously. The analgesic effect may be reduced and the duration of action curtailed with carbamazepine (an enzyme inducer) given concomitantly or previously.

Combination of mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, as the analgesic effect of a pure agonist may theoretically be attenuated in such circumstances.

Tramadol 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 medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants 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 or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

In individual cases, serotonin syndrome has been reported in temporal association with the therapeutic use of tramadol in combination with other serotonergic agents, e.g. selective serotonin reuptake inhibitors (SSRIs). Symptoms of serotonin syndrome include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. In general, discontinuation of serotonergic agents leads to a rapid improvement. Medicinal treatment to counteract such effects depends on the nature and severity of the symptoms.

Caution is required when co-administering tramadol and coumarin derivatives (e.g. warfarin), as increased INR values with severe bleeding and ecchymoses have been observed in some patients.

Other CYP3A4-inhibiting substances, such as ketoconazole and erythromycin, may inhibit both the metabolism of tramadol (N-demethylation) and possibly that of the active O-demethylated metabolite. The clinical significance of this interaction is not known.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre- or postoperative application of the antiemetic 5-HT<sub>3</sub> antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain. Although, no studies were performed to this, it can be assumed that other 5-HT<sub>3</sub> antagonists react in the same way with tramadol.

#### **4.6 Pregnancy and lactation**

Insofar as analgesic treatment with opioids is indicated during pregnancy, their use should be restricted to the administration of single doses. Chronic use of Tramadol Denk 50 is to be avoided throughout the entire pregnancy, as tramadol crosses the placenta and post-natal withdrawal phenomena may occur in the neonate due to habituation of the infant.

When given before or during childbirth, tramadol does not influence uterine contractility. In neonates, it can lead to changes in the respiratory rate, but these are generally without clinical significance.

Tramadol is excreted in human milk in very small amounts (approximately 0.1% of an intravenously administered dose). For this reason, tramadol should not be used during breast-feeding. Single administration of tramadol does not generally necessitate discontinuation of breast-feeding.

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

Even when used as directed, Tramadol Denk 50 can, as a result of drowsiness and blurred vision, alter responsiveness to such an extent that the ability to drive, use machines or perform hazardous tasks is impaired. This applies particularly at the start of treatment, when switching from another medication, in combination with other centrally acting medications and particularly in combination with alcohol.

#### **4.8 Undesirable effects**

The following categories are used when stating the frequency of undesirable effects:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

The most common undesirable effects occurring during treatment with Tramadol Denk 50 are nausea and dizziness, which occur in more than 1 in 10 patients.

##### Cardiovascular system

Uncommon: effect on circulatory regulation (palpitations, increased heartbeat, feelings of faintness and circulatory collapse). These undesirable effects can particularly occur in the upright posture and on physical exertion.

Rare: bradycardia, increase in blood pressure.

##### Central nervous system

Very common: dizziness.

Common: headache, light-headedness.

Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform seizures.

Respiratory depression can occur if the recommended doses are exceeded or other cerebral depressants are co-administered.

Epileptiform seizures have mainly occurred after administration of high tramadol dosages or after concomitant use of medicines that can themselves have a seizure-inducing effect or lower the seizure threshold.

#### *Metabolism and nutrition disorders:*

Unknown: hypoglycaemia

#### Psyche

Rare: hallucinations, confusion, sleep disorders and nightmares.

Psychiatric symptoms can occur following treatment with Tramadol Denk 50, which vary individually in intensity and nature (depending on personality and duration of administration). These may include mood changes (mostly elated, but also occasionally irritated mood), changes in activity levels (mostly suppression; occasionally increased) and changes in cognitive and sensory performance (altered perception and cognition, which may lead to errors in decision-making).

Dependence may develop.

#### Sensory organs

Rare: blurred vision.

#### Respiratory organs

Difficulty breathing and exacerbation of asthma have been reported, although no causal relationship could be established with the active substance tramadol.

#### Gastrointestinal tract

Very common: nausea.

Common: vomiting, constipation, dry mouth.

Uncommon: feeling of sickness, diarrhoea, stomach complaints (e.g. gastric pressure, bloatedness).

#### Skin and skin appendages

Common: sweating.

Uncommon: skin manifestations (e.g. pruritus, rash, flush).

#### Musculoskeletal system

Rare: reduced muscle strength.

#### Liver, gallbladder

Very rare: elevated transaminases.

#### Kidneys

Rare: micturition disturbances or reduced diuresis.

#### Overall health

Rare: allergic reactions (e.g. dyspnoea, wheezing, cutaneous swelling) and shock reactions (sudden circulatory failure) have occurred in very rare cases.

Dependence may develop if Tramadol Denk 50 is used over prolonged periods, although the risk is low. Withdrawal reactions can occur upon discontinuation of the medication.

## **4.9 Overdose**

### *Symptoms*

In general, symptoms as with other centrally acting analgesics (opioids) can be expected in cases of intoxication with tramadol. In particular, the following can be expected: miosis, vomiting, circulatory collapse, clouding of consciousness including comatose states, seizures and respiratory depression including respiratory paralysis.

### *Therapy*

General emergency procedures apply for maintaining airway patency (beware of aspiration) and respiratory/circulatory function, depending on the symptoms. Naloxone as an antidote for respiratory depression. In animal experimental studies, naloxone had no effect against seizures, for which diazepam IV should be used.

Tramadol is only poorly removed by dialysis. For this reason, haemodialysis or haemofiltration alone are not suitable for the treatment of acute intoxication with Tramadol Denk 50.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

ATC code: N02AX02

Tramadol is a centrally-acting opioid analgesic. It is a non-selective pure agonist for  $\mu$ -,  $\delta$ - and  $\kappa$ - opioid receptors, with greater affinity for  $\mu$  receptors. Other mechanisms contributing to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. Unlike morphine, tramadol has no respiratory depressant effect at analgesic doses over a wide range. Equally, gastrointestinal motility is not affected. Effects on the cardiovascular system tend to be minor. The potency of tramadol is reported to be  $1/10$  to  $1/6$  that of morphine.

### **5.2 Pharmacokinetic properties**

Over 90% of tramadol is absorbed following oral administration. Mean absolute bioavailability is approximately 70%, regardless of concomitant food intake. The difference between absorbed and unmetabolised available tramadol can probably be explained by a rather low first-pass metabolism. Following oral administration, first-pass metabolism is 30% maximum.

After oral administration (100 mg) in liquid form, the peak plasma concentration  $C_{\max}$  has been calculated at  $309 \pm 90$  ng/ml after 1.2 hours; after a similar dose in solid oral form,

$C_{\max}$  is  $280 \pm 49$  ng/ml after 2 hours. Tramadol has a high tissue affinity ( $V_{d,\beta} = 203 \pm 40$  l).

Binding to serum proteins is approximately 20%.

Tramadol crosses the blood-brain barrier and placenta. It is found in very small amounts in the breast milk together with its O-desmethyl derivative (0.1% and 0.02% of the administered dose, respectively).

The elimination half-life  $t_{1/2, \beta}$  is approximately 6 h, irrespective of the method of administration.

In patients over 75 years of age, it can be prolonged by a factor of about 1.4.

In humans, tramadol is largely metabolised by N- and O-demethylation, as well as by conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. Quantitatively speaking, there are considerable interindividual differences for the other metabolites. To date, 11 metabolites have been found in the urine. Based on findings from animal experiments, O-desmethyltramadol exceeds the potency of the parent substance by a factor of 2 - 4. Its half-life  $t_{1/2, \beta}$  (6 healthy subjects) is 7.9 h (range 5.4 - 9.6 h) and is of the same magnitude to that of tramadol.

Inhibition of isoenzymes CYP3A4 and/or CYP2D6, involved in the biotransformation of tramadol, can influence the plasma concentration of tramadol or that of its active metabolite. No clinically relevant interactions have been reported to date.

Tramadol and its metabolites are almost entirely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. If hepatic and renal function is impaired, a slight prolongation of half-lives can be anticipated. In patients with liver cirrhosis, elimination half-lives of  $13.3 \pm 4.9$  h (tramadol) and  $18.5 \pm 9.4$  h (O-desmethyltramadol) have been determined; in extreme cases, 22.3 h and 36 h, respectively. In patients with renal insufficiency (creatinine clearance  $< 5$  ml/min), the values were  $11 \pm 3.2$  h and  $16.9 \pm 3$  h, respectively; in extreme cases, 19.5 h and 43.2 h, respectively.

Within the therapeutic dose range, tramadol shows a linear pharmacokinetic profile.

The relation between serum concentrations and analgesic effect is dose-dependent, but with major variations in individual cases. A serum concentration of 100 - 300 ng/ml is generally effective.

### **5.3 Preclinical safety data**

Indications of mutagenic effects were seen in some *in vitro* test systems. *In vivo* investigations revealed no signs of mutagenic effects. Based on the data available, tramadol is to be rated as a non-mutagenic substance.

Studies on the tumorigenic potential of tramadol hydrochloride were conducted in rats and mice. The study in rats showed no evidence of any substance-related increase in tumour incidence. In the study on mice, increased incidence of hepatocellular adenomas in male animals (dose-dependently from 15 mg/kg, not significantly increased) was observed, as well as an increase in pulmonary tumours among female animals in all dose groups (significantly, but not dose-dependently increased).



In reproductive toxicity studies, tramadol dosages from 50 mg/kg daily caused maternotoxic effects in rats and led to an increase in neonatal mortality. In the progeny, retardation in the form of impaired ossification occurred, as well as delayed vaginal and eye opening. No teratogenic effects were observed. The fertility of male rats was not adversely affected. Females showed a lower pregnancy rate after higher dosages (from 50 mg/kg per day). In rabbits, maternotoxic effects and skeletal anomalies occurred in the progeny at doses of 125 mg/kg or more.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

The excipients are lactose monohydrate, macrogol 6000, aspartame, citric acid, sodium hydrogen carbonate, sodium carbonate, sodium sulphate, sodium cyclamate, orange flavouring, povidone (K 25), simethicone (2E,4E)-hexa-2,4-dienoic acid-methyl cellulose-water.

### **6.2 Incompatibilities**

Not known.

### **6.3 Shelf life**

The shelf life is 3 years.

### **6.4 Special precautions for storage**

Store in a dry place below 25 °C.

Do not use Tramadol Denk 50 after the expiry date which is stated on the carton.

Store in the original package. Keep the tube tightly closed in order to protect the content from moisture.

Keep out of the reach and sight of children.

### **6.5 Nature and contents of container**

White, synthetic polypropylene tube with polyethylene desiccant stopper.

Original pack of 10 effervescent tablets.

Free medical samples of 10 effervescent tablets.

### **6.6 Special precautions for disposal and other handling**

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

## **7. Marketing authorisation holder**

DENK PHARMA GmbH & Co. KG  
Prinzregentenstr. 79  
81675 München  
Germany

**8. Marketing authorisation number in Germany**

34728.00.00

**9. Date of authorisation in Germany**

30/10/1995

**10. Date of revision of the text**

February 2015

**11. General classification for supply**

Medicinal product subject to medical prescription