SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Tramal Denk 100 mg
Tramal Denk 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: tramadol hydrochloride

Tramal Denk 100 mg
Each prolonged-release tablet contains 100 mg tramadol hydrochloride.
Excipient with known effect: Each prolonged-release tablet contains 2.55 mg lactose monohydrate.

Tramal Denk 200 mg
Each prolonged-release tablet contains 200 mg tramadol hydrochloride.
Excipient with known effect: Each prolonged-release tablet contains 2.51 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Tramal Denk 100 mg prolonged-release tablets are round, biconvex, white coloured film-coated tablets, marked with the manufacturer‘s logo ♎ on one side, marked with T1 on the other side.

Tramal Denk 200 mg prolonged-release tablets are round, biconvex, slightly brownish orange coloured film-coated tablets, marked with the manufacturer‘s logo ♎ on one side, marked with T3 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Posology
The dose 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. Daily doses of 400 mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed, Tramal Denk should be administered as follows:

Adults and adolescents above the age of 12 years
The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily (see section 5.1).

Tramal Denk should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Tramal Denk is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Paediatric population
Tramal Denk is not suitable for children below the age of 12 years.

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

Patients with 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. In cases of severe renal and/or severe hepatic insufficiency Tramal Denk prolonged-release tablets are not recommended.

Method of administration
The tablets are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.

4.3 Contraindications

Tramal Denk is contraindicated:
- in hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or other psychotropic medicinal products
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5)
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory center or function, increased intracranial pressure.

In patients sensitive to opiates tramadol should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Tramal Denk should only be carried out for short periods under strict medical supervision.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with 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.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

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 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.

Caution should be exercised during concomitant treatment with tramadol 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 4.8).

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT_3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Tramal Denk should not be used in pregnant women.
Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding
During lactation about 0.1% of the maternal dose is secreted into the milk. Tramal Denk is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

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

Even when taken according to instructions, tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:

Very common:	≥1/10
Common:	≥1/100 to <1/10
Uncommon:	≥1/1000 to <1/100
Rare:	≥1/10 000 to <1/1000
Very rare:	<1/10 000
Not known:	frequency cannot be estimated from the available data

Immune system disorders
Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

Cardiac disorders
Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare: bradycardia
Investigations
Rare: increase in blood pressure

Vascular disorders
Uncommon: cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Nervous system disorders
Very common: dizziness
Common: headache, somnolence
Rare: paraesthesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders

Convulsion occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see section 4.4 and 4.5).

Metabolism and nutrition disorders
Rare: changes in appetite
Not known: hypoglycaemia

Psychiatric disorders
Rare: hallucination, confusional state, sleep disturbance, delirium, anxiety and nightmares
Psychic adverse reactions may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually euphoric mood, 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, hallucination, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusional state, delusions, depersonalization, derealization, paranoia).

Eye disorders
Rare: miosis, vision blurred, mydriasis

Respiratory, thoracic and mediastinal disorders
Rare: respiratory depression, dyspnoea
If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.
Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders
Very common: nausea
Common: constipation, dry mouth, vomiting
Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous tissue disorders
Common: hyperhidrosis
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders
Rare: motorial weakness
Hepatobiliary disorders
In a few isolated cases increased hepatic enzyme has been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders
Rare: micturition disorder (dysuria and urinary retention)

General disorders
Common: fatigue

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 national reporting system.

4.9 Overdose

Symptoms
In principle, on intoxication with tramadol 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 open the respiratory tract (aspiration!), maintain respiration and circulation depending on the symptoms.

The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication with oral formulations, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol 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. Therefore treatment of acute intoxication with Tramal Denk with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC code: N02AX02

Tramadol is a centrally-acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ 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 and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory-depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Paediatric population
Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

5.2 Pharmacokinetic properties

More than 90% of tramadol hydrochloride is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. 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 %.

Tramadol has a high tissue affinity ($V_{d,ß}$ = 203 ± 40 l). It has a plasma protein binding of about 20 %.
After administration of tramadol hydrochloride 100 mg the peak plasma concentration C_{max} = 141 ± 40 ng/ml is reached after 4.9 h; after administration of tramadol hydrochloride 200 mg C_{max} 260 ± 62 ng/ml is reached after 4.8 h.
Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life $t_{1/2,ß}$ is approximately 6 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.

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. Its 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. Up to now, clinically relevant interactions have not been reported.
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 case of impaired hepatic or 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.

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.

Paediatric population
The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male and female fertility was not affected. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tramal Denk 100 mg
Tablet core:
microcrystalline cellulose
hypromellose
magnesium stearate
colloidal anhydrous silica

Film coating:
hypromellose
lactose monohydrate
macrogol 6000
propylene glycol
talc
titanium dioxide

Tramal Denk 200 mg
Tablet core:
microcrystalline cellulose
hypromellose
magnesium stearate
colloidal anhydrous silica

Film coating:
hypromellose
lactose monohydrate
macrogol 6000
propylene glycol
talc
titanium dioxide
quinoline yellow, aluminium salt
red iron oxide
brown iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Tramal Denk is available in PVC/PVDC/ aluminium blisters.
Pack size: 30 prolonged-release tablets.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal 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

100 mg: 37294.00.00
200 mg: 37294.02.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

25.06.1996

10. DATE OF REVISION OF THE TEXT

July 2017

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription