

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Doloforte Denk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: tramadol + paracetamol.

Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light-yellow, oblong, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doloforte Denk is indicated for the symptomatic treatment of moderate to severe pain.

The use of Doloforte Denk should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see also section 5.1).

Doloforte Denk is recommended for adults and adolescents 12 years or older.

4.2 Posology and method of administration

Posology

Adults and adolescents (12 years and older)

The use of Doloforte Denk should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see section 5.1).

The dose should be individually adjusted according to intensity of pain and response of the patient.

An initial dose of two film-coated tablets of Doloforte Denk is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Doloforte Denk should under no circumstances be administered for longer than is strictly necessary (see also section 4.4 – Special warnings and precautions for use). If repeated use or long term treatment with Doloforte Denk is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Children

The effective and safe use of Doloforte Denk has not been established in children below the age of 12 years. Treatment is therefore not recommended in children below the age of 12 years.

Elderly patients

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 17% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses should be not less than 6 hours, due to the presence of tramadol.

Renal insufficiency

Because of the presence of tramadol, the use of Doloforte Denk is not recommended in patients with severe renal insufficiency (creatinine clearance < 10 ml/min). In cases of moderate renal insufficiency (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency

In patients with severe hepatic impairment Doloforte Denk should not be used (see section 4.3). In moderate cases prolongation of the dosage interval should be carefully considered (see section 4.4).

Method of administration

Oral use

The film-coated tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs
- Doloforte Denk should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5. Interactions with other medicinal products and other forms of interaction)
- Severe hepatic impairment
- Epilepsy not controlled by treatment (see section 4.4).

4.4 Special warnings and precautions for use

Warnings

- In adults and adolescents 12 years and older. The maximum dose of 8 film-coated tablets of Doloforte Denk should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol containing products concurrently without the advice of a physician.

- In severe renal insufficiency (creatinine clearance <10 ml/min), Doloforte Denk is not recommended.
- In patients with severe hepatic impairment Doloforte Denk should not be used (see section 4.3). The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.
- In severe respiratory insufficiency, Doloforte Denk is not recommended.
- Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.
- Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Doloforte Denk only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Precautions for use

Doloforte Denk should be used with caution in opioid dependent patients, or in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported (see section 4.8).

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur (see section 4.8).

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:

- *Non-selective MAO inhibitors*
Risk of serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- *Selective-A MAO inhibitors*
Extrapolation from non-selective MAO inhibitors:
Risk of serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- *Selective-B MAO inhibitors*
Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol.

Concomitant use is not recommended with:

- *Alcohol*
Alcohol increases the sedative effect of opioid analgesics.
The effect on alertness can make driving of vehicles and the use of machines dangerous.
Avoid intake of alcoholic drinks and of medicinal products containing alcohol.
- *Carbamazepine and other enzyme inducers*
Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.
- *Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)*
Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which needs to be taken into consideration:

- In isolated cases there have been reports of Serotonin Syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates:
Increased risk of respiratory depression which can be fatal in cases of overdose.
- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.
These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Doloforte Denk and warfarin like compounds are administered concurrently due to reports of increased INR.
- Other drugs 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.
- Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Since Doloforte Denk is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

- *Data regarding paracetamol:*
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.
- *Data regarding tramadol:*
Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol 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. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Breast-feeding

Since Doloforte Denk is a fixed combination of active ingredients including tramadol, it should not be ingested during breast-feeding.

- *Data regarding paracetamol:*
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast-feeding by women using single ingredient medicinal products containing only paracetamol.
- *Data regarding tramadol:*
Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be ingested during breast-feeding.

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: 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), including isolated reports.

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/tramadol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

Cardiovascular system disorders:

Uncommon: hypertension, palpitations, tachycardia, arrhythmia.

Central and peripheral nervous system disorders:

Very common: dizziness, somnolence

Common: headache, trembling

Uncommon: involuntary muscular contractions, paraesthesia, tinnitus

Rare: ataxia, convulsions.

Metabolism and nutrition disorders:

Unknown: hypoglycaemia

Psychiatric disorders:

Common: confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders

Uncommon: depression, hallucinations, nightmares, amnesia

Rare: drug dependence

Post marketing surveillance

Very rare: abuse.

Vision disorders:

Rare: blurred vision.

Respiratory system disorders:

Uncommon: dyspnoea.

Gastro-intestinal disorders:

Very common: nausea

Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence

Uncommon: dysphagia, melaena.

Liver and biliary system disorders:

Uncommon: hepatic transaminases increase.

Skin and appendages disorders:

Common: sweating, pruritus

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

Urinary system disorders:

Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).

Body as a whole:

Uncommon: shivers, hot flushes, thoracic pain.

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

Tramadol

- Postural hypotension, bradycardia, collapse.
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Rare cases: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases: changes in appetite, motor weakness, and respiratory depression.
- Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). 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).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Symptoms of withdrawal reactions, 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 if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
- There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

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 their national reporting system.

4.9 Overdose

Doloforte Denk is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol:

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.

Symptoms of overdose from paracetamol:

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Emergency treatment:

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions.
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Doloforte Denk with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥ 150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram).

Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tramadol, combinations
ATC code: N02AX52

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists of the μ , δ , and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastrointestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Doloforte Denk is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

5.2 Pharmacokinetic properties

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 μ g/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives $t_{1/2}$ are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of tramadol/paracetamol (37.5 mg/325 mg), no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %.

After administration of tramadol/paracetamol (37.5 mg/325 mg), the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of tramadol/paracetamol (37.5 mg/325 mg) with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Doloforte Denk can be taken independently of meal times.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}=203 \pm 40$ l). It has a plasma protein binding of about 20%.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Biotransformation

Tramadol is extensively metabolized after oral administration. About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol is metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys.

The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of paracetamol is excreted unchanged in urine.

In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

No preclinical study has been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility, reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. No effect on fertility has been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Pregelatinised maize starch
Microcrystalline cellulose
Sodium starch glycolate (type A)
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxides (yellow) (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Aluminium/PVC blisters

Pack size: 20 film-coated tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER IN GERMANY

92337.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

17.06.2015

10. DATE OF REVISION OF THE TEXT

April 2015

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.