SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TRAMADOL DENK 50mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Effervescent tablet contains 50mg Tramadol hydrochloride

Excipients with known effect: Each effervescent tablet contains 75mg lactose (as lactose monohydrate) and approximately 214mg sodium (see section 4.4)

3 PHARMACEUTICAL FORM

Effervescent tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management (treatment and prevention) of moderate to severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with tramadol in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

Dosage and administration:
As with all analgesic drugs, the dose of Tramadol Hydrochloride 50mg Effervescent Tablets should be adjusted according to the intensity of the pain
and the sensitivity of the individual patient. The lowest effective dose foranalgesia should generally be selected. The total daily dose of 400 mg active substance should not be exceeded, except in special circumstances.

Adults and children aged 12 years and over:
Depending upon the severity of the pain, the initial dose is 50 or 100mg followed by 50 or 100mg not more frequently than 4 hourly. For acute pain aninitial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100mg at 4 - 6 hourly intervals, and duration of treatment should be matched to clinical need (see section 5.1) For pain associated with chronic conditions an initial dose of 50mg is advised. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4). Treatment periods should usually be limited and intermittent. Treatment should be given only where there exists a medical need. A total oral daily dose of more than 400mg is not usually required.

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 yearselimination may be prolonged. Therefore, if necessary the dosage interval is to beextended according to the patient's requirements.

It should be noted that in volunteers aged over 75 years the elimination half-life Tramadol was increase by 17% following oral administration.

Renal insufficiency / renal dialysis/ 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 carefullyconsidered according to the patient's requirements.

For patients with creatinine clearance <30 ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renalimpairment (creatinine clearance <10 ml/min).

In severe hepatic impairment the dosage interval should be increase to 12hours.

Paediatric population:
Not recommended for children under 12 years of age.

Method of administration
The tablets should be dissolved in at least 50 ml water before administration, independently of meals.

Treatment goals and discontinuation
Before initiating treatment with Tramadol Hydrochloride 50mg Effervescent Tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility

of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

Tramadol Hydrochloride is contraindicated :

- in hypersensitivity to the active substance or to any of the excipients listed insection 6.1
- in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or other psychotropic medicinal drugs
- in common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment
- in patients with the hereditary metabolic disease phenylketonuria. Themedicinal product contains the sweetener aspartame

4.4 Special warnings and precautions for use

Warnings:
Tolerance, psychic and physical dependence may develop, especially after long-term use. For this reason the clinical need for continued analgesic treatment should be carried out for short periods under strict medical supervision and reviewed regularly. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tramadol Hydrochloride. Repeated use of Tramadol Hydrochloride can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tramadol Hydrochloride may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).Before initiating treatment with Tramadol Hydrochloride and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Concomitant use of Tramadol Hydrochloride and sedating medicinal products such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol Hydrochloride concomitantly with sedating medicinal products, the lowest effective dose of Tramadol Hydrochloride 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).

Tramadol Hydrochloride 50mg Effervescent Tablets is not suitable as a substitute in opioid dependent patients. Although it is an opioid agonist, Tramadol Hydrochloride 50mg Effervescent Tablets cannot suppress morphine withdrawal symptoms.

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

CYP2D6 metabolism:
Tramadol 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. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children:
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events.
Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function:
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Precautions for use:
Tramadol Hydrochloride 50mg Effervescent Tablets should be used with particular

caution in patients with head injury, opioid-dependent patients, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

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. At therapeutic doses respiratory depression has infrequently been reported.

Convulsions have been reported in patient receiving tramadol at therapeutic doses and the risk may be increased at doses exceeding the recommended upper daily dose limit (400 mg). Patients with a history of epilepsy or susceptibility to seizures should be treated with Tramadol Hydrochloride 50mg Effervescent Tablets only if there are compelling reasons to do so.

In addition the risk of convulsions may increase in patients taking Tramadol Hydrochloride 50mg Effervescent Tablets and concomitant medication that can lower the seizure threshold (see section 4.5).

In one study use of Tramadol Hydrochloride 50mg Effervescent Tablets during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available use of Tramadol Hydrochloride 50mg Effervescent Tablets during light planes of general anaesthesia should be avoided.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

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 If

serotonin syndrome is suspected, a dose reduction or discontinuation of

therapy should be considered depending on the severity of the symptoms.
Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

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.

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.
Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with tramadol. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.
Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Each tablet contains approximately 214mg sodium. This should be borne in mind when using Tramadol Hydrochloride 50mg Effervescent Tablets in patients on a low sodium diet.

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

Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

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 Hydrochloride 50mg Effervescent Tablets with other centrally acting drugs including alcohol may potentiate CNS depressant effects (see section 4.8).
The concomitant use of Tramadol Hydrochloride 50mg Effervescent tablets with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

The results of pharmacokinetic studies have so far shown that on the concomitant or Simultaneous administration or previous administration with cimetidine (enzyme inhibitor) is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the Tramadol Hydrochloride 50mg Effervescent Tablets dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Simultaneous or previous administration of carbamazepine (enzyme inducer) markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur. There is a theoretical possibility that tramadol could interact with lithium and 5HT and noradrenaline potentiating ant-depressants due to their respective mechanisms of action. There have been no reports of this potential interaction.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 syndrome, a potentially life-threatening condition (see section 4.4 and 4.8)

Quinidine has been reported to increase the Cmax and AUC of tramadol approximately 25%. However, these increases fell within the normal therapeutic range for tramadol and no dosage adjustment is required.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and Tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.
In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the 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-HT3 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. Animal studies (rats and rabbits, exposure to tramadol up to 7 times that expected in man) have not revealed teratogenic effects and minimal embryotoxicity (delayed ossification). Fertility, reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy therefore Tramadol Hydrochloride 50mg Effervescent Tablets should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available. 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.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Breast-feeding:
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk and may cause respiratory depression in the infant. In the immediate post- partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast- fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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 Hydrochloride 50mg Effervescent Tablets may cause drowsiness and dizziness and therefore may impair the reactions of drivers and machine operators, this effect may be potentiated by alcohol and other CNS depressants or psychotropic substances.

Ambulant patients should be warned not to drive or operate machinery if affected.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a

of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

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, <1/10

Uncommon: ≥1/1000,

Rare: ≥1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data

Cardiovascular disorders:

uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare: bradycardia

Investigations:

Rare: increase in blood pressure

Nervous system disorders
Tiredness, drowsiness, which in most instances followed intravenous use, havebeen rarely reported.

very common: dizziness

common: headache,
somnolence

rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal

coordination and syncope; speech disorders.

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

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

not known: Serotonin syndrome,

Psychiatric disorder:
rare: hallucinations, confusion, sleep disturbance , anxiety and nightmares. Psychic adverse reactions may occur following administration of tramadol which vary individually I intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionallyincrease) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders)..

Frequency unknown: drug dependence (see section 4.4)

Eye disorders:
rare: blurred vision, miosis, mydriasis

Respiratory disorders:
rare : respiratory depression; dyspnoea
Worsening of asthma has been reported, though a causal relationship has notbeen established.

Frequency unknown:

HiccupsGastrointestinal

disorders:

very common: nausea
common: vomiting, constipation, dry mouth
uncommon: retching; gastrointestinal irritation (a feeling of pressure in thestomach, bloating), diarrhoea

Skin and subcutaneous disorders:

common: sweating
uncommon:dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:

rare: motorial weakness

Hepatobiliary disorders:
In a few isolated cases an increase in liver enzyme values has been reported ina temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:
rare: micturition disorders (difficulty in passing urine, dysuria and urinaryretention)

Metabolism and nutrition disorders:
not known: hypoglycaemia

General disorders:

common: fatigue

Uncommon: drug withdrawal syndrome

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 with tramadol discontinuationinclude: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Immune system disorders:

rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneuroticoedema) and anaphylaxis.

Drug dependence
Repeated use of Tramadol Hydrochloride 50mg Effervescent Tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Physical dependence:
Abuse and withdrawal reactions include agitation , anxiety, nervousness,insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Other adverse events:
Diaphoresis has been reported Flushing have been rarely reported. Cases of blood dyscrasias have been rarely observed during treatment with tramadol,but causality has not been established.

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 balanceof the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdosage:
In principle, on intoxication with tramadol Symptoms of overdosage and typical of other centrally acting (opioid) analgesics to be expected, and these include in particular, miosis, vomiting, cardiovascular collapse, sedation and consciousness disorders up to coma, seizures, convulsion and respiratory depression up to respiratory arrest.

Therapeutic measures in overdosage:
Supportive and general emergency measures such as keep open the respiratory tract (aspiration!), maintain respiration, the patency of the airway and maintaining cardiovascular function should be instituted. Depending on the symptoms, naloxone should be used to reverse respiratory depression. In animal experiments, naloxone had no effect on convulsions, in such cases fits can be controlled with diazepam given intravenously.

In case of intoxication orally, 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 Tramadol Hydrochloride Effervescent Tablets 50mg with haemodialysis or haemofiltration alone is not suitable for detoxification.

Overdose
Serotonin syndrome has also been reported.

5.1 Pharmacodynamic properties

Tramadol Hydrochloride 50mg Effervescent Tablets is a centrally acting analgesic. It is non selective pure agonist at mu, delta and kappa opioid with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibitor of neuronal reuptake 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

The half life of the terminal elimination phase (t1/2ß) was 6.0 ± h in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, t1/2ß was 7.0 ± 1.6 on oral administration. Since tramadol is eliminated both metabolically and renally, the terminal half-life t1/2ß may be prolonged in impaired hepatic or renal function. However, the increase in the t1/2ß values is relatively if at least one of these organs is functioning normally. In patients with liver cirrhosis t1/2ß tramadol was a mean of 13.3 ± 4.9 h; inpatients with renal insufficiency (creatinine clearance <5 ml/min) it was 11.0 ± 3.2 h.
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.

More than 90% of Tramadol Hydrochloride 50mg Effervescent Tablets 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 %.

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 Cmax of 280 to 208 mcg/L and Tmax of 1.6 to 2h.

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 t1/2,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 Odesmethyltramadol 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 t1/2,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.

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.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The relationship between serum concentrations and the analgesic effect is dosedependent, 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 Odesmethyltramadol 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

In single and repeat-dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatotoxicity) is observed. 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. Symptoms of toxicity are typical of opioids and include restlessness, salivation, ataxia, vomiting, tremor, reduced weight gain, dyspnoea and convulsions. 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.

Exposure to tramadol (≤ that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a battery of in-vitro and in vivo mutagenicity tests were negative. 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.

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

fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

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, nonsignificant 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

Citric acid
Sodium hydrogen carbonate
Lactose monohydrate
Sodium sulfate
Sodium carbonate
Povidone
Sodium cyclamate
Aspartame
Macrogol
Orange Flavouring
Simethicone emulsion
Water
Isopropanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store 25°C. Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene tube with polyethylene stopper containing silica gel as desiccant.

6.6 Special precautions for disposal

Dissolve effervescent tablets in a glass of water prior to intake.

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

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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Denk Pharma GmbH & Co Kg - Prinzregenten Str 79 81675 Munchen, Germany

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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