TRAMADEX®
PHYSICIAN'S LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

Tramadex tablets
Tramadex drops, oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance: tramadol hydrochloride

One tablet contains 100 mg of tramadol hydrochloride
Drops, oral solution 100 mg per 1 ml oral solution (= 40 drops)

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORMS

Tablets.
Drops, oral solution.

4. CLINICAL PARTICULARS

4.1. Indications

Short to medium term treatment of moderate to severe pain

4.2. Posology and method of administration
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. Unless otherwise prescribed, *Tramadex* should be administered as follows:

Adults and adolescents above the age of 14 years:

Tramadex tablets, 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.
Tramadex drops*,* 50-100 mg tramadol hydrochloride 4-6 hourly.

For doses not practicable with this strength, other strengths of this medicinal product are available.

Tablets are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.
Drops are to be taken with a little liquid or dripped on some sugar, independent of meals.
The lowest analgesically effective dose should generally be selected. Daily doses of 400 mg active substance should not be exceeded, except in special clinical circumstances.

Tramadex should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with *Tramadex* 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.

Children

Tramadex is not suitable for children below the age of 14 years

Geriatric patients:

In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, however, a dose adjustment is not usually necessary in elderly 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.
Higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia.
For elderly patients **over 75 years old**, total dose should not exceed 300 mg/day.

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 interval should be carefully considered according to the patients requirements. In cases of severe renal and/or severe hepatic insufficiency *Tramadex* is not recommended.
With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

4.3. Contraindications

Tramadol is contraindicated

- In hypersensitivity to tramadol or any of the excipients (see section 6.1) or opioids.
- In acute intoxication with alcohol, hypnotics, analgesics, narcotics, centrally acting analgesics, opioids or other psychotropic medicinal products. *Tramadex* may worsen central nervous system and respiratory depression in these patients.
- 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 special precautions for use

Tramadex may only be used with particular caution in opioid-dependent patients, patients with shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function.

Tramadex should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving *Tramadex*.

In patients sensitive to opiates the product 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. In these patients alternative non-opioid analgesics should be considered. When large doses of *Tramadex* are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

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). Concomitant use of *Tramadex* increases the seizure risk in patients taking:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics).
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.).
- Other opioids.

Administration of *Tramadex* may enhance the seizure risk in patients taking:

- MAO inhibitors,
- Neuroleptics, or
- Other drugs that reduce the seizure threshold (see section 4.5).

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections).

Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

In *Tramadex* overdose, naloxone administration may increase the risk of seizure.

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 *Tramadex* should only be carried out for short periods under strict medical supervision.

Tramadol is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *Tramadex* in situations

where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Tramadex could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

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

Tramadex tablets/drops contain Sucrose. Patients with rare hereditary problems of Fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine.

Suicide Risk

- Do not prescribe *Tramadex* for patients who are suicidal or addiction-prone.
- Prescribe *Tramadex* with caution for patients who are taking tranquilizers or antidepressant drugs and patients who use alcohol in excess and who suffer from emotional disturbance or depression. Serious potential consequences of overdose with *Tramadex* are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see section 4.9).
- Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including *Tramadex*, particularly with concomitant use of serotonergic drugs (see section 4.5)

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with *Tramadex*. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive *Tramadex*.

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of over dosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants,

antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

Serious potential consequences of overdosage with *Tramadex* are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment.

Withdrawal symptoms may occur if *Tramadex* is discontinued abruptly. Reported symptoms have included anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been reported less frequently with *Tramadex* discontinuation include panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering *Tramadex* at the time of discontinuation.

The administration of *Tramadex* may complicate the clinical assessment of patients with acute abdominal conditions.

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

Tramadex 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 *Tramadex*.

Concomitant administration of Tramadex with other centrally depressant medicinal products including alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics may potentiate the CNS effects (see section 4.8). *Tramadex* increases the risk of CNS and respiratory depression in these patients.

Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

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. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of *Tramadex* and carbamazepine is not recommended.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist like tramadol may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotoninergic drugs, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants, α2-adrenergic blockers, mirtazapine, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort, drugs which impair metabolism of serotonin (including MAOIs), and drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) may cause serotonin toxicity. This may occur within the recommended dose. If concomitant treatment of *Tramadex* with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Serotonin syndrome may include mental-status changes (e.g., confusion, agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, sweating), neuromuscular aberrations (e.g., hyperreflexia, incoordination, myoclonus) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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^{o}C and inducible or ocular clonus.

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

Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.
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.

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors, such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome.

Administration of CYP3A4 inducers, such as rifampin and St. John's Wort, with *Tramadex* may affect the metabolism of tramadol leading to altered tramadol exposure.

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.

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

4.6. Pregnancy and lactation

Animal studies with tramadol revealed at very high doses effects on organ development, ossification, reduction in neonatal body weight 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 *Tramadex* should not be used in pregnant women.
Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

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. Tramadex should not be used prior to or during labor unless the potential benefits outweigh the risks. Chronic use during pregnancy may lead to physical dependence and neonatal withdrawal symptoms.

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

4.7. Effects on ability to drive and use machines

Even when taken according to instructions, *Tramdex* 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, <1/10
Uncommon:	≥1/1000, <1/100
Rare:	≥1/10000, <1/1000
Very rare:	<1/10000
Not known	cannot be estimated from the available data

Immune system disorders:
Uncommon: toxic epidermal necrolysis (TEN) and Stevens-Johnson-syndrome (SJS), and cross reactivity with non-steroidal anti-inflammatory drugs

Cardiovascular disorders:

Common: hot flushes, vasodilation

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. Myocardial infarction, peripheral ischemia, hypertension, hypertension aggravated.

Rare: bradycardia

Nervous system disorders:

Very common: dizziness/vertigo

Common: headache, drowsiness, somnolence, hypoesthesia

Uncommon: sedation, disturbance in attention, dizziness aggravated

Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, hypertonia and dysgeusia. 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: speech disorders, abnormal gait, amnesia, difficulty in concentration, movement disorder, euphoria, emotional lability, delirium, paresthesia

Psychiatric disorders:

Common: depression, restlessness

Uncommon: irritability, libido decreased, disorientation, abnormal dreams

Rare: hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic adverse reactions may occur following administration of *Tramadex* which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Dependence may occur. Suicidal ideation, drug abuse and addiction.

Eye disorders:

Common: miosis, visual disturbance
Rare: blurred vision

Not known: mydriasis

Respiratory disorders:

Common: sneezing, cough, rhinorrhea, nasal congestion, sinus congestion

Uncommon: yawning

Rare: dyspnoea. Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:

Very common: nausea

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

Uncommon: anorexia, retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhea, flatulence, toothache, constipation aggravated, appendicitis, pancreatitis

Not known: sore throat

Skin and subcutaneous tissue disorders:

Common: sweating, dermatitis

Uncommon: dermal reactions (e.g. pruritus, rash, urticaria), contusion, piloerection, clamminess, night sweats

Not known: Vesicles

Musculo-skeletal disorders:

Common: arthralgia, back pain, pain in limb, neck pain

Uncommon: muscle cramps, muscle spasms, joint stiffness, muscle twitching, myalgia, osteoarthritis aggravated

Rare: motorial weakness

Hepatobiliary disorders:

Uncommon: cholelithiasis, cholecystitis

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

Renal and urinary disorders:

Common: Urinary frequency

Uncommon: hematuria

Rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention)

Reproductive system and breast disorders:

Common: menopausal symptoms

Rare: menstrual disorders

Infections and infestations:

Common: nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis

Uncommon: cellulitis, ear infection, gastroenteritis, pneumonia, viral infection

General disorders:

Common: fatigue, asthenia, malaise, weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain, blood creatine phosphokinase increased, appetite decrease

Uncommon: feeling jittery, edema lower limb, shivering, joint swelling, drug withdrawal syndrome, peripheral swelling, joint sprain, muscle injury, alanine aminotransferase increased, blood pressure increased, aspartate aminotransferase increased, heart rate increased, blood glucose increase, liver function tests abnormal

Rare: weight loss, allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; 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 discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, derealization, paranoia)

Not known: accidental injury, death, serotonin syndrome, flushing, hypoglycaemia

Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently in patients taking tramadol during clinical trials and/or reported in post-marketing experience. A causal relationship between Tramadol and these events has not been determined.
Aabnormal ECG, hypotension, myocardial ischemia, pulmonary edema, pulmonary embolism, migraine, gastrointestinal bleeding, liver failure, proteinuria, hepatitis, stomatitis, Creatinine increase, hemoglobin decrease, cataracts, deafness

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, respiratory depression up to respiratory arrest, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, cardiac arrest, and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol. Review of case reports has indicated that the risk of fatal overdose is further

increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Treatment

In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The stomach is to be emptied by vomiting (conscious patient) or gastric irrigation. While naloxone will reverse some, but not all, symptoms caused by over dosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice.

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 haemo-filtration. Therefore treatment of acute intoxication with Tramadex with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N 02 AX 02

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 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.

5.2. Pharmacokinetic properties

More than 90% of *Tramadex* 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 *Tramadex* 100 mg the peak plasma concentration C_{max} =141 + 40 ng/ml is reached after 4.9 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 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 dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

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 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.

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

Tramadex tablets

Calcium hydrogen phosphate dihydrate, sucrose, guar gum, povidone, talc, ammonio methacrylate copolymer, calcium stearate, calcium carbonate, polyacrylate, silica colloidal anhydrous, maize starch, macrogol 6000, mannitol, acacia, yellow lake E104, titanium dioxide, carboxymethylcellulose sodium, propylene glycol, iron oxide red E172, shellac, carnauba wax, castor oil

Tramadex drops (oral solution)

Purified water, sucrose, propylene glycol, glycerol, sodium cyclamate, saccharin sodium, potassium sorbate, macrogolglycerol hydroxystearate, mint oil, anise flavour artificial.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Tramadex tablets: 36 months.
Tramadex drops: 36 months (before opening), 6 months upon first opening.

6. 4. Special precautions for storage

Store below 25^{o}C.

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