SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zeridame SR 100mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 100mg tramadol hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Zeridame SR 100mg Prolonged Release Tablets are off white, round biconvex tablets, 9.1 mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment 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 hydrochloride in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

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

Unless otherwise prescribed, Zeridame SR Prolonged Release Tablets should be given as follows:

Adults and adolescents older than 12 years:
The usual initial dose is 100mg, twice daily, in the morning and evening. Dependent upon the needs of the patient, subsequent doses may be administered earlier than 12 hours, but must not be administered earlier than 8 hours after the previous dose. **Under no circumstances should more than two doses be taken in any one 24 hour period.**
If the painkilling is insufficient, the dose may be increased to:
150mg, twice daily or
200mg, twice daily.

The smallest effective analgesic dose should always be used. Daily doses of 400 mg of active substance must not be exceeded, unless exceptional medical reasons require so.

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

Paediatric population
Zeridame SR is not suitable for children under the age of 12 years.

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

Renal insufficiency/dialysis and hepatic impairment

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

Method of administration

Zeridame SR Prolonged Release Tablets should be swallowed completely, without breaking or chewing, independent of meals, with sufficient liquid.

Treatment goals and discontinuation

Before initiating treatment with Zeridame SR, 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

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs.
- patients receiving MAO – inhibitors, or within 2 weeks of their withdrawal.
- patients with epilepsy not adequately controlled by treatment
- opioid withdrawal treatment.

4.4 Special warnings and precautions for use

Zeridame SR should only be used following a strict benefit – risk evaluation and appropriate precautionary measures in the following cases: in patients dependent on opioids, patients suffering head injuries, shock, decreased level of consciousness of unknown origin, disturbances of the respiratory centre or function, or increased intracranial pressure, patients with moderate to severe impaired liver or kidney function.

Zeridame SR should not be used in combination with alcohol.

In patients sensitive for opioids the medicine should be used cautiously.

Concomitant use of Zeridame SR and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Zeridame SR concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of 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).

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg).
The risk on convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold. (see section 4.5).
Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons.

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 Zeridame SR. Repeated use of Zeridame SR 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 Zeridame SR 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 Zeridame SR 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.

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 hydrochloride.

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.

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.

Tramadol is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Fatal cases of unintended overdose are reported to be related with the use of other psycho-active medicines or substances including alcohol. Tramadol should be prescribed with care in alcoholics and users of other psycho-active drugs.

After long term treatment (> 3 months) of analgesics with use every second day or more frequently, headache may develop or aggravate. Cases of medication overuse headache (MOH) have been reported following not registered use of tramadol in the treatment of tension or cluster headache or migraine. Headache caused by overuse of analgesics should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

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.

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.

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.

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
Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

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.

4.5 Interaction with other medicinal products and other forms of interaction

MAO – inhibitors
Zeridame SR should not be combined with MAO-inhibitors (see section 4.3). Life threatening interactions affecting the central nervous system as well as respiratory and cardiovascular function have been observed in patients who have been treated with MAO inhibitors within 14 days prior to the administration of the opioid pethidine. The same interactions with Zeridame SR as with MAO inhibitors cannot be ruled out.

Other centrally acting active substances
In concomitant use of Zeridame SR and other centrally acting drugs, including alcohol, a potentiation of CNS effects should be taken into consideration (See section 4.8).
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
The concomitant use of Zeridame SR with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Enzyme inhibitor / inducer
The results of pharmacokinetic research, so far, showed that no interactions need to be expected in concomitant or prior use of cimetidine (enzyme inhibitor).
The concomitant or prior use of carbamazepine (enzyme inducer) may reduce the analgesic effectiveness and shorten the duration of the action.

Mixed opioid agonists / antagonists
The combination of mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended because it is theoretically possible that the analgesic effect of a pure agonist is attenuated under these circumstances.

Serotonergic agents / Seizure threshold lowering drugs
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 sections 4.4 and 4.8).

Coumarin derivatives
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.

CYP3A4 Inhibitors
Other medicinal products with a known inhibiting effect on CYP3A4, such as ketoconazole and erythromycin, could inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of the active O-demethyl-metabolite. The clinical relevancy of this interaction has not been investigated. (See section 4.8).

Ondansetron
The analgesic effect of Tramadol is in part mediated by inhibition of the reuptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre – or postoperative application of the antiemetic 5 – HT_3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

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.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Animal tests with very large concentrations of tramadol showed effects on the development of the organs, bone formation and mortality of the neonate. Teratogenic effects have not been found. Tramadol crosses the placenta, insufficient experience is available on the chronic use of tramadol during

pregnancy. Tramadol – administered before or during birth – does not affect uterine contractility.

Breast-feeding

Administration to nursing women is not recommended as tramadol hydrochloride may be secreted in breast milk and may cause respiratory depression in the infant.

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. 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.

4.7 Effects on ability to drive and use machines

Zeridame SR has minor or moderate influence on the ability to drive and use machines. It may cause drowsiness and blurred vision. This is especially applicable in combination with other psychotropic drugs, and alcohol. 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

Undesirable effects reported are listed according to the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders
Unknown: Hypoglycaemia

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

Nervous system disorders
Very common: dizziness.
Common: headache, drowsiness.
Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, and syncope.
Not known: Serotonin syndrome.
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 drugs, which can lower the seizure threshold or themselves induce cerebral convulsions (see section 4.4 and section 4.5).

Psychiatric disorders
Rare: hallucinations, confusion, anxiety, sleep disturbances and nightmares.
Psychic side-effects may 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).
Unknown: drug dependence (see section 4.4), abuse and addiction may occur.

Eye disorders
Rare: blurred vision.
Not known (cannot be estimated from the available data: mydriasis.

Cardiac and vascular disorders
Uncommon: effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia, increase in blood pressure.

Respiratory, thoracic and mediastinal disorders
Worsening of asthma has also been reported, though a causal relationship has not been established.
Not known: Hiccups.

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

Hepatobiliary disorders

Very rare: an increase in liver enzyme values has been reported after use of tramadol.
Skin and subcutaneous tissue disorders
Common: sweating.
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders
Rare: motorial weakness.

Renal and urinary disorders
Rare: micturition disorders (difficulty in passing urine and urinary retention).

General disorders and administration site conditions
Common: fatigue.
Uncommon: drug withdrawal syndrome.

Drug dependence
Repeated use of Zeridame SR 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.

Physical Dependence
Dependence, abuse, addiction, and withdrawal reactions may occur. Symptoms which occur on withdrawal, mainly identical to withdrawal symptoms with opioids, may be: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro intestinal symptoms.
Very rare*:* atypical withdrawal symptoms have been reported: panic attack, severe anxiety, hallucinations, paraesthesia, tinnitus, and other unusual central nervous system symptoms.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms
In tramadol intoxication, in principle, the same symptoms occur as for all other central acting analgesics (opioids). In particular, these include miosis, vomiting, cardiovascular collapse, narrowing of consciousness leading to coma, convulsions, respiratory depression leading to respiratory failure.

Serotonin syndrome has also been reported.

Treatment
General emergency measures are applicable.
Maintenance of the airway (aspiration), maintenance of respiration and cardiovascular circulation depending on the symptoms.
Emptying of the stomach by means of vomiting (patient to be conscious) or by means of pumping the stomach. Consideration should also be given to the administration of activated charcoal, if necessary via the stomach pump tube. Depending how long has elapsed from ingestion, administration of a suitable laxative to speed up elimination should be considered. In the event that the patient's consciousness is reduced, intubation prior to performing these procedures is essential.

The antidote for respiratory depression is naloxone.
In animal tests naloxone proved to be ineffective against convulsions.
In that case diazepam should be administered intravenously.

Tramadol is only minimally removed from plasma using haemodialysis, haemofiltration or haemoperfusion.

Therefore treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not a suitable way of detoxification. Administration of a suitable laxative may help to speed up elimination of unabsorbed tramadol, if administered early after overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other opioids, ATC code: N 02 AX 02

Mechanism of action

Tramadol is a centrally acting opioid analgesic.
It is a non-selective, partial agonist of μ-, δ- and κ-opioid receptors with a higher affinity for μ-receptors. Other mechanisms contributing to the analgesic effect are the inhibition of the neural noradrenaline reuptake, and an enhanced release of serotonin.

Pharmacodynamic effects / Clinical efficacy and safety

Tramadol has an antitussive action.

Contrary to morphine tramadol does not suppress respiration in analgetic doses over a large range.

The action on the cardiovascular system is minimal.

The potency of tramadol is reported to be 1 / 10 to 1 / 6 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

Absorption

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

The difference between absorbed and non – metabolised available tramadol is probably due to low first – pass effect. The first pass – effect after oral administration is a maximum of 30 %.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 l). Protein binding is about 20 %.

After administration of Tramadol 100 mg SR Tablets the maximum peak plasma concentration C_{max} 141 ± 40 ng / ml is reached after 4.9 hours. After administration of Tramadol 200 mg SR Tablets a C_{max} 260 ± 62 ng / ml is reached after 4.8 hours.

Tramadol passes the blood – brain and placenta barrier. Very small amounts of the substance and its O – demethyl derivative are found in the breast – milk (0.1 % and 0.02 % respectively of the applied dose).

Biotransformation

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 $t_{½β}$ (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 cytochrome p450 isoenzymes, cyp3a4 and cyp2d6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

Elimination

Elimination of half-life $t_{½β}$ 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 1.4.

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.

Linearity

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

Pharmacokinetic / pharmacodynamics relationship

The relationship between serum concentrations and the analgesic effect is dose – dependent, but varies considerably in isolated cases. A serum concentration of 100 – 300 ng / ml is usually effective.

Paediatric population

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

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

5.3 Preclinical safety data

In repeated oral and parenteral administration of tramadol during 6 to 26 weeks to rats and dogs, as also during 12 months to dogs, there are no indications for changes caused by the substance in haematological, clinical – chemical and histological experiments.

Only after high doses, far above the therapeutic doses, central symptoms occurred: restlessness, salivation, convulsion, reduced increase in weight.
Rats and dogs tolerate the oral dose of 20 mg / kg resp 10 mg / kg bodyweight, dogs also tolerate 20 mg / kg bodyweight, rectally administered.

Tramadol doses as from 50 mg / kg / day cause intoxication of the mother, in rats, and result in an increased mortality in newborn rats.
In young rats development disorders occurred as ossification disturbances, delayed opening of the vagina and eyes.

The fertility of male rats was not influenced.

However the percentage of females with young reduced after high dosages (as of 50 mg / kg / day).

In rabbits, toxic effects occurred as of 125 mg / kg in the mother and skeletal anomalies in the offspring.

In some *in – vitro* test systems there is report on mutagenic effects.
In *in – vivo* experiments there was no indication for mutagenic effects.
On the basis of the knowledge available up till now it is unclear whether tramadol possesses mutagenic potential.

Experiments have been performed on rats and mice with regard to the tumuorigenic potential of tramadol.

From tests in rats it could not be shown that the substance increases the chance of tumours.

In tests in mice an increased incidence of liver – cell adenomas in males (depending on the dose, with an insignificant increase as of 15 mg / kg) and an increased chance of lung tumours in females in all dose selections (significant, but not dose dependent) was found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate (E341),

Hydroxypropylcellulose (E463),

Colloidal anhydrous silica (E551),

Magnesium stearate (E470b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

PP / PE tablet container: 6 months after opening

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al / clear PVC blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.

Al / opaque PVC child resistant blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.

Polypropylene tablet container with polyethylene tamper evident closure containing 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No Special Requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/1113

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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