SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tramadex OD 100
Tramadex OD 200
Tramadex OD 300

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tramadex OD 100: prolonged-release tablets: Each tablet contains 100 mg of tramadol hydrochloride.
Tramadex OD 200: prolonged-release tablet: Each tablet contains 200 mg of tramadol hydrochloride.
Tramadex OD 300: prolonged-release tablet: Each tablet contains 300 mg of tramadol hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.
White to off-white, plain, bevelled edge, round biconvex tablet.

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see section 4.5].
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
Limit dosages and durations to the minimum required.
Follow patients for signs and symptoms of respiratory depression and sedation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Posology

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total daily dose of 400 mg of tramadol should not be exceeded, except in special circumstances.

Alternative tablet strengths of Tramadex OD are available. Where necessary, appropriate tablet strengths should be used to achieve the required dose.

Tramadex OD should be taken once every 24 hours as follows:

Adults and adolescents (14 years and over):

The starting dose is one 100 mg prolonged-release tablet once daily. The usual dose is one 200 mg prolonged-release tablet once daily, to be taken preferably in the evening. If this

does not provide sufficient pain relief, the dosage can be increased in 100 mg dose increments to 300 mg or to a maximum of 400 mg once daily.

Paediatric population:
Tramadex OD is not recommended for the treatment of children under 14 years of age.

Elderly:
A dose adjustment is not usually necessary in patients up to 75 years of age without clinically manifest hepatic or renal insufficiency.
In patients over 75 years, the elimination half-life of tramadol may be prolonged. Use in these patients is not recommended.

Renal impairment, 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.
Tramadex OD must not be used in patients with severe hepatic impairment or with severe renal impairment (creatinine clearance <10 ml/min) (see section 4.3). Caution is advised in patients with moderate hepatic or moderate renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

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

Duration of administration
Tramadex OD should not be used for a period longer than absolutely necessary. If continued pain treatment is necessary due to the nature and severity of the illness, careful regular surveillance should be carried out (including periods without treatment, if necessary) in order to determine the need for continued treatment.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute intoxication or overdose with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products).
- Patients receiving concomitant treatment with MAO inhibitors or who have been treated with MAO inhibitors during the past 2 weeks (see section 4.5).
- Severe hepatic or severe renal impairment (creatinine clearance < 10ml/min).
- Epilepsy not adequately controlled by treatment (see section 4.4).
- For use in narcotic withdrawal treatment.
- Tramadol must not be administered during breast-feeding if long-term treatment is necessary (see section 4.6).

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

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 new-born 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.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of tramadol 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 tramadol 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).

Patients with respiratory depression or patient taking concomitant CNS depressant drugs
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.

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.

Precautions
Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, increased intracranial pressure, impairment of hepatic or renal function, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function and in diabetic patients because of the occurrence of hypoglycaemia with tramadol.

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

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol must 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 OD.

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

Mixed agonist-antagonists (buprenorphine, nalbuphine and pentazocine): Concomitant treatment with tramadol is not recommended because theoretically, this could reduce the analgesic effects of the pure agonist due to competitive blocking of receptors, resulting in the risk of occurrence of withdrawal symptoms.

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.

Sedative medicines such as benzodiazepines or related drugs: 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 the duration of concomitant use should be limited (see section 4.4). The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Other CNS depressants: Opioid analgesics, barbiturates, benzodiazepines, sedative antidepressants, sedative H1 antihistamines, anxiolytics other than benzodiazepines, hypnotics, neuroleptics, centrally acting antihypertensives, thalidomide, baclofen: Increased risk of central nervous system depression. The resulting impaired reaction time can make driving and operating machinery dangerous.

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).

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. Tramadol readily crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore, tramadol should not be used in pregnant women.

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.

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.

Breast-feeding:
Administration to nursing women is not recommended as tramadol 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.

If long-term treatment after birth is necessary, breastfeeding is contraindicated (see section 4.3).

Fertility:
Post marketing surveillance of tramadol 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

Tramadol may cause dizziness and/or drowsiness and has, even when used according to the directions, an influence on the ability to drive and use machines. This effect may occur at the beginning of treatment, and in particular in conjunction with other psychotropic substances, particularly alcohol.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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

4.8 Undesirable effects

The most commonly reported undesirable effects, nausea and dizziness, have been observed in more than 10% of patients.

The frequencies are defined as follows:

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

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

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

Psychiatric disorders
Rare: hallucinations, confusion, sleep disturbance, nightmares, anxiety, delirium.

After the administration of tramadol, in rare cases, various psychiatric adverse events may occur, the nature and severity of which vary between patients (depending on the individual reactivity and the duration of treatment). These include mood changes (usually euphoria, occasionally dysphoria), changes in activity (usually reduced activity, occasionally an increase) and changes in cognitive and sensory capacities (for example the ability to make decisions, perception problems) may be observed. Drug dependence may occur.

Not known: drug dependence (see section 4.4)

Nervous system disorders
Very common: dizziness.
Common: headache, somnolence.
Rare: speech disorders, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
Not known: serotonin syndrome.

Convulsions primarily occurred following administration of high doses of tramadol or following concomitant treatment with medicinal products that lower the seizure threshold or trigger seizures (see sections 4.4 and 4.5).

Eye disorders
Rare: vision blurred, miosis, mydriasis.

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

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

Respiratory, thoracic and mediastinal disorders
Rare: respiratory depression, dyspnoea.

Respiratory depression may occur if the quantities administered greatly exceed the recommended doses and in the case of concomitant administration of other CNS depressant substances (see section 4.5).

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

Not known: hiccups.

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

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

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

Musculoskeletal and connective tissue disorders
Rare: muscular weakness.

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

General disorders and administration site conditions
Common: fatigue.
Uncommon: drug withdrawal syndrome.
Symptoms of drug withdrawal syndrome, similar to those observed during opioid withdrawal may occur, such as agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms. Other symptoms of withdrawal have also been reported very rarely, including: panic attack, severe anxiety, hallucination, paraesthesia, tinnitus and other unusual CNS problems (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Investigations
Rare: increase in blood pressure.

<u>Reporting of suspected adverse reactions</u>
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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, loss of consciousness leading to coma, convulsions, respiratory depression up to respiratory arrest.

Serotonin syndrome has also been reported.

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.

Treatment
General emergency measures are applicable: including maintenance of respiratory and cardiocirculatory functions. The antidote for respiratory depression is naloxone. There is a risk of increased convulsions with the use of naloxone. In animal tests naloxone proved to be ineffective against convulsions. In that case diazepam should be administered 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. This must not delay the (repeated) administration of activated charcoal to prevent the absorption of tramadol.

Tramadol is only minimally removed from plasma using haemodialysis or haemofiltration. Therefore treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not a suitable way of detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, Other opioids
ATC code: N02A X02

Tramadol is a centrally acting opioid analgesic. It is a pure non-selective μ, δ and κ opioid receptor agonist with a higher affinity for μ receptors. Other mechanisms responsible for the analgesic effects of tramadol include the inhibition of the neuronal re-uptake of noradrenalin and an increase in serotonin release.

Tramadol has an antitussive effect. Also, gastrointestinal motility is less affected. The effects on the cardiovascular system tend to be slight. Tramadol has 1/10 (1 tenth) to 1/6 (one sixth) the potency 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

Following oral administration of a single dose, Tramadex OD is almost completely absorbed (>90%). The mean absolute bioavailability is approximately 70%, independent of food intake. The difference between the tramadol absorbed and the non-metabolised available tramadol is probably due to a weak first-pass effect. The first-pass effect following oral administration is a maximum of 30%.

Tramadol has a high tissue affinity (volume of distribution = 203 ± 40 litres). Approximately 20% is bound to plasma proteins.

Following single-dose administration of one 200 mg Tramadex OD prolonged-release tablet, in a fasted state, a mean maximum plasma concentration (C_{max}) of 241 ± 62 ng/ml is reached after a median time (t_{max}) of 6.0 hours.

Tramadol crosses the blood-brain barrier and the placenta. Very small quantities of the active substance and its O-demethylated derivative have been found in breast milk (0.1% and 0.02% of the administered dose respectively).

The elimination half-life is approximately 6 hours, regardless of route of administration. In patients over 75 years of age the half-life can be prolonged by a factor of approximately 1.4.

In humans, tramadol is mainly metabolised by N- and O-demethylation and by conjugation of the O-demethylation products with glucuronic acid. Only the O-desmethyltramadol metabolite is pharmacologically active. Considerable quantitative inter-individual differences have been observed between the other metabolites: 11 different metabolites have been identified to date in urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent molecule by a factor of 2 to 4. Its half-life (6 healthy volunteers) is 7.9 hours (range 5.4 to 9.6 hours), similar to 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 wholly excreted in urine. Cumulative urinary excretion accounts for 90% of the total radioactivity of the administered dose. The half-life may be slightly longer in the case of hepatic or renal impairment.
In patients with liver cirrhosis, an elimination half-life of 13.3 ± 4.9 hours (tramadol) and 18.5 ± 9.4 hours (O-desmethyltramadol) has been observed, with one extreme case of elimination half-lives of 22.3 and 36 hours respectively. In renal insufficiency patients

(creatinine clearance < 5 ml/min), elimination half-lives of 11 ± 3.2 and 16.9 ± 3 hours respectively have been observed, with one extreme case of 19.5 and 43.2 hours respectively. Tramadex OD has a linear pharmacokinetic profile within the therapeutic dosing range.

The relationship between serum concentration and analgesic effect is dose-dependent but varies considerably between individuals. A serum concentration of 100 ng/ml to 300 ng/ml is usually effective.

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

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

5.3 Preclinical safety data

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

In rats, doses of tramadol greater than or equal to 50 mg/kg/day caused toxic effects in pregnant animals and an increase in neonatal mortality. Retarded growth in the form of abnormal ossification and delayed vaginal and ocular opening were observed in the progeny. There was no change in the fertility of male animals. After higher doses (≥ 50 mg/kg/day), females showed a reduced gestation level.

In rabbits, toxic effects were revealed in the mothers and skeletal abnormalities in the progeny above doses of 125 mg/kg. Signs indicating a mutagenic effect were found in certain in vitro tests, but in vivo studies did not show any such effects. Based on findings to date, tramadol can be regarded as non-mutagenic.

Studies were conducted in rats and mice on the carcinogenic potential of tramadol hydrochloride. The study in rats did not show any indication of an increased frequency of tumours linked to the active substance. In the study on mice, an increased frequency of hepatocellular adenomas was observed in male animals (a dose-dependent nonsignificant increase above 15 mg/kg) and an increase in pulmonary tumours in females for all dosage groups (significant but not dose-dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polyvinyl acetate, xanthan gum, hydroxypropyl distarch phosphate (E1442) (Contramid®), povidone, hydrogenated vegetable oil, magnesium stearate, silica colloidal anhydrous, sodium laurilsulfate.

6.2 Incompatibilities
Not applicable

6.3 Shelf-life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Blister.
Pack sizes: 2, 5, 10, 20, 30 or 150 prolonged-release tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION NUMBER
Tramadex OD 100: 139-25-31580-00
Tramadex OD 200: 139-26-31581-00
Tramadex OD 300: 139-27-31582-00

8. MARKETING AUTHORISATION HOLDER
Dexcel Pharma Technologies Ltd.
21 Haftzadi Nahum Street, Jerusalem 9548402, Israel

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