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: One prolonged-release tablet contains 100 mg tramadol hydrochloride.
Tramadex OD 200: One prolonged-release tablet contains 200 mg tramadol hydrochloride.
Tramadex OD 300: One prolonged-release tablet contains 300 mg 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 severity of pain and the response of the individual patient.

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.
In general, the lowest effective analgesic dose should be chosen. A daily dose of 400 mg of tramadol should not be exceeded except in special clinical cases.

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.

Children (under 14):
Tramadex OD is not recommended for the treatment of children (under 14 years of age).

Elderly patients:
Dose adjustment in elderly patients (up to 75 years of age) without clinically relevant hepatic or renal impairment is normally not necessary. 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 is not recommended for 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
The tablets should be swallowed whole, with a sufficient quantity of liquid and not divided crushed or chewed. The tablets can be taken with or without food.

4.3 Contraindications
- Hypersensitivity to tramadol or to any of the excipients listed in section 6.1.
- Acute intoxication or overdose with CNS depressants (alcohol, hypnotics, other opioid analgesics, etc.).
- 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).
- Tramadol must not be administered during breastfeeding if long-term treatment, is necessary (see section 4.6).

4.4 Special warnings and precautions for use
Consumption of alcohol is not recommended during treatment with tramadol. Concomitant treatment with carbamazepine is not recommended (see section 4.5).

Warnings:
Tolerance and psychic and physical dependence may develop, especially after long-term use. At therapeutic doses, withdrawal symptoms have been reported with a frequency of 1 in 8,000 while reports of dependence and abuse have been less frequent.

Because of the potential for dependence or withdrawal to occur, the clinical need for continued analgesia should be reviewed regularly. In patients with a tendency to drug abuse or dependence, tramadol should only be used for short periods under strict medical surveillance.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

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

Respiratory depression or patient taking CNS depressants:
Caution is recommended with administration of tramadol in patients at risk for respiratory depression or receiving medicinal products likely to produce respiratory depression.

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 should be used with caution in patients with head trauma, increased intracranial pressure, impairment of hepatic or renal function, in patients in shock, an altered state of consciousness (with no obvious cause), respiratory centre disorders or respiratory dysfunction and in diabetic patients because of the occurrence of hypoglycemia with tramadol.

There is an increased risk of seizures if the tramadol dose exceeds the maximum recommended daily dose (400 mg). Seizures have been reported at the therapeutic doses. Patients with controlled epilepsy or patients with a known risk of seizure should only be treated with tramadol in cases of absolute necessity. There is an increased risk of seizures in patients taking concomitant medications which lower the seizure threshold (see section 4.5).

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

Concomitant medication contraindicated during treatment with tramadol
Tramadol must not be used in combination with selective or nonselective MAO inhibitors (see section 4.3).

Concomitant medication not recommended during treatment with tramadol
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.

Alcohol: Alcohol increases the sedative effect of opioid analgesics. The resulting drowsiness can be dangerous while driving or operating machinery. Alcoholic beverages and medicinal products containing alcohol should not be consumed during treatment with tramadol (see section 4.7).

Carbamazepine (enzyme inducer): Possibility of decreased plasma concentrations of tramadol and its pharmacologically active metabolite, resulting in reduction of the analgesic effect.

Naltrexone: Use of tramadol with naltrexone may reduce the analgesic effect. If necessary the analgesic dose can be increased.

Concomitant medication to be used with care during tramadol treatment
Other morphine derivatives (including antitussives and substitution treatments) benzodiazepines, barbiturates: Major risk of respiratory depression, can be fatal in case of overdose.

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).

Venlafaxine: Risk of convulsions.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

4.6 Fertility, pregnancy and lactation

Fertility:
No fertility studies have been conducted with Tramadex OD.

Pregnancy:
Tramadol should not be used during pregnancy unless clearly necessary. In humans, there is insufficient data available to appropriately assess the safety of tramadol use in pregnant women.

As with other opioid analgesics:
- Tramadol crosses the placental barrier.
- Chronic use of tramadol may induce – at any dosage – a withdrawal syndrome in newborns.
- At the end of pregnancy, high dosages, even for short-term treatment, may induce respiratory depression in the newborn.

Animal studies have not shown any teratogenic effects, but at high doses, foetotoxicity due to maternotoxicity appeared (see section 5.3).

Breast Feeding:
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).

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 may be potentiated by alcohol and concomitant use of other CNS-depressants or antihistamines. If patients are affected they should be warned not to drive or operate machinery.

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, <1/10
Uncommon:	≥1/1,000, <1/100
Rare:	≥1/10,000, <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, angioedema) and anaphylactic reaction.

Metabolism and nutrition disorders

Rare: appetite disorder.
Not known: hypoglycemia.

Psychiatric disorders

Rare: hallucinations, confusional state, 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). Mood disorders (usually euphoria, occasionally dysphoria), changes in activity (usually reduced activity, occasionally an increase) and, altered cognitive and sensory capacities (for example the ability to make decisions, perception problems) may be observed. Dependence may occur.

Symptoms of drug withdrawal syndrome, similar to those observed during withdrawal of opiates may occur, such as agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor, and gastro-intestinal symptoms. Other symptoms of withdrawal have also been reported, including: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and other CNS problems

Nervous system disorders

Very common: dizziness.
Common: headaches, somnolence
Rare: paraesthesia, tremor, convulsions.
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.

Cardiac disorders
Uncommon: effects on cardiovascular regulation (palpitations, tachycardia). These undesirable effects occur in particular after intravenous administration and in patients undergoing physical exertion.
Rare: bradycardia.

Vascular disorders
Uncommon: effects on cardiovascular regulation (orthostatic hypotension or circulatory collapse). These undesirable effects occur in particular after intravenous administration and in patients undergoing physical exertion.

Respiratory, thoracic and mediastinal disorders
Rare: respiratory depression.
Respiratory depression may occur if the quantities administered greatly exceed the recommended doses and in the case of concomitant administration of other CNS depressant medicinal products (see section 4.5).
Unknown: Hiccups
An aggravation of asthma has been reported although a causal relationship was not confirmed.

Gastrointestinal disorders
Very common: nausea.
Common: vomiting, constipation, dry mouth.
Uncommon: gastrointestinal tract irritation (abdominal discomfort, flatulence).

Hepatobiliary disorders
In some isolated cases, an increase in hepatic enzymes was reported during the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders
Common: hyperhidrosis.
Uncommon: skin reaction (for example pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders
Rare: muscular weakness.

Renal and urinary disorders
Rare: micturation problems (dysuria and urinary retention).

General disorders and administration site conditions
Common: fatigue.

Investigations
Rare: blood pressure increased.

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. 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 leading to respiratory failure.
Serotonin syndrome has also been reported.

Treatment
General emergency measures are applicable: including maintenance of respiratory and cardiocirculatory functions.

Emptying of the stomach by means of vomiting (patient to be conscious) or by means of pumping the stomach. Gastric lavage can be considered if the ingestion of overdose is very recent. This must not delay the (repeated) administration of activated charcoal to prevent the absorption of tramadol. 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.

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 analgesic. It is a pure non-selective μ, delta and k morphine receptor agonist with a higher affinity for μ receptors. Other mechanisms responsible for the product's analgesic effects include the inhibition of the neuronal re-uptake of noradrenalin and an increase in serotonin release.

Tramadol has an antitussive effect. Unlike morphine, broad ranges of analgesic tramadol doses do not have any respiratory depressant effect. Nor is there any effect on gastro-intestinal motility. The effects on the cardiovascular system tend to be slight. Tramadol has 1/10 to 1/6 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 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 (Cmax) of 241 ± 62 ng/ml is reached after a median time (tmax) 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. The half life can be prolonged by a factor of approximately 1.4 in patients over 75 years of age.

In man, tramadol is extensively 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. Tests on animals showed 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 cytochrome CYP3A4 and/or CYP2D6, the isozymes responsible for biotransformation of tramadol could modify 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 (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 presents a linear pharmacokinetic profile within the recommended therapeutic dosing regimen.

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
Preclinical data reveal no special risk for clinical use based on acute toxicity, repeated dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies. Animal studies have not shown any teratogenic effects, but at high doses, foetotoxicity due to maternotoxicity appeared.

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 ingredient. In the study on mice, an increased frequency of hepatocellular adenomas was observed in male animals (non significant dose-dependent increase above 15 mg/kg) and an increase in pulmonary tumours in females for all dosage groups (significant but non dose-dependent increase).

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
Tramadex OD 200: 139-26-31581
Tramadex OD 300: 139-27-31582

8. MARKETING AUTHORISATION HOLDER
Dexcel Pharma Technologies Ltd.
1 Dexcel Street, Or Akiva 3060000, Israel

Revised in February 2022 according to MOH guidelines