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מרץ 2015

TRAMADEX OD 100, 200, 300

צוות רפואי נכבד,

חברת דקסל פארמה טכנולוגיות בע"מ מבקשת להודיעכם על עדכון בעלון לרופא של התכשיר:
טרמדקס OD 100, 200, 300 (Tramadex OD 100, 200, 300), טבליות בשחרור מושהה

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פנייה לבעל הרישום: דקסל פארמה טכנולוגיות בע"מ, רח' דקסל 1, אור-עקיבא 3060000, ישראל, טל': 04-6364000.

החומר הפעיל והחוזק:

Tramadol Hydrochloride 100/200/300mg

התוויה מאושרת:

Treatment of moderate to severe pain.

העלון עודכן באוגוסט 2014. העדכון הינו בסעיפים הבאים:

4.2 Posology and method of administration
The dosage should be adjusted according to the severity of pain and the response of the individual patient.
The tablets should be swallowed whole, with a sufficient quantity of liquid and not divided or chewed.
The tablets can be taken with or without food.

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 or chewed.
The tablets can be taken with or without food.

4.3 Contraindications
Known hypersensitivity to tramadol, ~~or to~~ any of the excipients or opioids.
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).
Concomitant treatment with linezolid (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, i.e. more than 2 to 3 days, is necessary (see section 4.6).
Tramadex OD is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment.
Tramadex OD is also contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment.
Do not prescribe **Tramadex OD** for patients who are suicidal or addiction-prone.

4.4 Special warnings and special 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:
~~Tramadol has a low potential for dependence. However,~~ With long-term use, tolerance and psychological and/or physical dependence may develop, even at therapeutic doses. 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.

Tramadol is an opioid agonist of the morphine type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.
Like other opioid agonists, legal or illicit, tramadol can be abused. This should be considered when prescribing or dispensing **Tramadex OD** in situations where the healthcare professional is concerned about a risk of misuse, abuse, or diversion.
Tramadex OD could be abused by breaking, crushing, chewing, or dissolving the product which can result in the uncontrolled delivery of the opioid, and as a consequence poses a significant risk of overdose and death.
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Tramadol is not suitable as a substitute in opioid dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms. At therapeutic doses, withdrawal symptoms have been reported with a frequency of 1 in 8,000 (see section 4.8) while reports of dependence and abuse have been less frequent.
Withdrawal symptoms may occur if **Tramadex OD** is discontinued abruptly. Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous opioid therapy.(See section 4.8 undesirable effects).
Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy.

Suicide Risk
- Do not prescribe **Tramadex OD** for patients who are suicidal or addiction-prone.
- Prescribe **Tramadex OD** with caution for patients who are taking tranquilizers or antidepressant drugs and patients who use alcohol in excess and who suffer from emotional disturbance ~~or~~

~~depression~~. Serious potential consequences of overdosage with **Tramadex OD** are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see section 4.9).

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

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

Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses above the recommended range. Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking:

- Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.
- Monoamine Oxidase (MAO) inhibitors
- Neuroleptics, or
- Other drugs that reduce the seizure threshold (such as bupropion, mirtazapine, tetrahydrocannabinol).

Risk of convulsions may also be increased in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, certain metabolic disorders, alcohol and drug withdrawal and CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizures.

The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including Tramadex OD, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, mirtazapine and triptans, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within the recommended dose.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphroesis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38ºC and inducible or ocular clonus.

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

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

Tramadol products in excessive doses, either alone or in combination with other Central Nervous System (CNS) depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to

the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

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

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

Precautions:
Tramadol should be used with caution in patients with head trauma~~,~~ and increased intracranial pressure. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving Tramadex OD.
Tramadol should be used with caution in patients with 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, in diabetic patients because of the occurrence of hypoglycemia with tramadol and in elderly patients due to the risk of loss of consciousness and falls.

Caution should be used when selecting the dose for an elderly patient. Usually, dose administration should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant medication contraindicated during treatment with tramadol
Tramadol must ~~should~~ not be used in combination with selective or nonselective MAO inhibitors. Serotonin Syndrome (diarrhoea, tachycardia, sweating, tremor, confusion and coma) may develop (see section 4.3).
Linezolid: Treatment experience with non-selective MAOI indicates a risk of development of Serotonin Syndrome: diarrhoea, tachycardia, sweating, tremor, confusion and coma.

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.~~
Patients taking carbamazepine, a CYP3A4 inducer**,** may have a significantly reduced analgesic effect. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of **Tramadex OD** and carbamazepine is not recommended.

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.

~~Selective serotonin re-uptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and anti-depressants: Risk of convulsions and/or serotonin syndrome.~~

~~Medicinal products that reduce seizure threshold, notably tricyclic antidepressants (imipramines), selective serotonin re-uptake inhibitors (SSRIs), neuroleptic antidepressants (phenothiazine, butyrophenone),~~ ~~mefloquine, bupropion: Increased risk of convulsions.~~

Antagonistic interaction exists between 5-HT3 antagonists and tramadol with the risk of decreasing/weakening effect of tramadol.

Venlafaxine: Risk of convulsions and/or Serotonin Syndrome.

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.

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

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

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

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 toxicity

There have been postmarketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and α2-adrenergic blockers. Caution is advised when **Tramadex OD** is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant treatment of **Tramadex OD** with a drug affecting the serotonergic

neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Tramadex OD should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these 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.

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported during post-marketing surveillance of tramadol immediate-release products.

The effect of Tramadex OD, if any, on the later growth, development and functional maturation of the child is unknown.

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

Breast Feeding ~~Lactation~~:
Tramadex OD is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.
Tramadol and its metabolites have been detected in human breast milk in small amounts. An infant could ingest 0.1% of the single dose given to the mother. A single administration of tramadol does not usually require breastfeeding to be interrupted. If repeated administration is needed for several days, i.e. more than 2 to 3 days,
breastfeeding should be suspended. 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 ~~to operate machinery~~
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.

Cardiac disorders
Uncommon (~~<1%~~ ≥1/1,000, <1/100): effects on cardiovascular regulation (palpitations, tachycardia, orthostatic hypotension or cardiovascular collapse). These undesirable effects occur in particular after intravenous administration and in patients undergoing physical exertion.
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): bradycardia, increase in blood pressure.
Not known (cannot be estimated from the available data): hypotension.

Nervous system disorders
Very common (~~>10%~~ ≥1/10): dizziness.
Common (~~1-10%~~ ≥1/100, <1/10): headaches, confusion, tremor, Somnolence, vertigo.
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): changes in appetite, paraesthesia, ~~tremor,~~ respiratory depression, epileptiform seizures.
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).
Epileptiform seizures 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).
Not known (cannot be estimated from the available data): loss of consciousness, ataxia, disturbance in attention, dysarthria, gait abnormal, headache aggravated, mental impairment, sedation, sleep apnea syndrome, syncope.

Psychiatric disorders
Common (≥1/100, <1/10): anxiety, insomnia
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): hallucinations, confusion, sleep disturbance, nightmares.
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 and drug abuse may occur.
Not known (cannot be estimated from the available data): abnormal behavior, agitation, depression, emotional disturbance, euphoric mood, indifference, irritability, libido decreased, nervousness.

Eye disorders
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): blurred vision.
Not known (cannot be estimated from the available data): visual disturbance.

Respiratory, thoracic and mediastinal disorders
An aggravation of asthma has been reported although a causal relationship was not confirmed.
Not known (cannot be estimated from the available data): dyspnea.

Gastrointestinal disorders
Very common (~~>10%~~ ≥1/10): nausea, constipation.
Common (~~1-10%~~ ≥1/100, <1/10): vomiting, ~~constipation,~~ dry mouth, diarrhea, dyspepsia, abdominal pain.
Uncommon (~~<1%~~ ≥1/1,000, <1/100): gastro-intestinal irritation (a feeling of gastric heaviness, flatulence).
Not known (cannot be estimated from the available data): abdominal discomfort, abdominal distension, abdominal tenderness, change in bowel habit, constipation aggravated, diverticulitis, diverticulum, dyspepsia aggravated, dysphagia, fecal impaction, gastric irritation, gastritis, gastrointestinal hemorrhage, gastro-esophageal reflux disease, lower abdominal pain, pancreatitis aggravated, rectal hemorrhage, rectal prolapse, retching, blood in stool.

Skin and subcutaneous tissue disorders
Common (~~1-10%~~ ≥1/100, <1/10): sweating, pruritus.
Uncommon (~~<1%~~ ≥1/1,000, <1/100): dermal reactions (for example ~~pruritus,~~ rash, urticaria).
Not known (cannot be estimated from the available data): allergic dermatitis, cold sweat, dermatitis, night sweats, pallor, generalized pruritus.

Musculoskeletal and connective tissue disorders
Common (≥1/100, <1/10): arthralgia
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): muscular weakness.
Not known (cannot be estimated from the available data): muscle cramps.

Hepatobiliary disorders
Not known (cannot be estimated from the available data): biliary tract disorder, cholelithiasis, alanine

aminotransferase decreased, alanine aminotransferase increased, aspartate aminotransferase decreased, aspartate aminotransferase increased,
~~In some isolated cases, an increase in hepatic enzymes was reported during the therapeutic use of tramadol.~~

Renal and urinary disorders
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): micturation problems (difficulty in passing urine and urinary retention).
Not known (cannot be estimated from the available data): urinary hesitation.

General disorders and administration site conditions
Common (≥1/100, <1/10): Fatigue, weakness
Rare (~~<0.1%~~ ≥1/10,000, <1/1,000): hypersensitivity/allergic reactions (for example dyspnoea, bronchospasm, wheezing, Quincke's oedema), ~~and~~ anaphylaxis. Withdrawal symptoms similar to those observed during withdrawal of opiates may occur, such as agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor, sweating, rigors, pain, nausea, diarrhea, upper respiratory symptoms, piloerection, restlessness, lacrimation, rhinorrhea, yawning, chills, myalgia, and mydriasis. irritability, backache, joint pain, weakness, abdominal cramps, anorexia, vomiting, increased blood pressure, respiratory rate, or heart rate, and gastro-intestinal symptoms. Other symptoms of withdrawal have also been reported, including: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and other CNS problems.
Not known (cannot be estimated from the available data): asthenia and malaise.

Metabolism and nutrition disorders
Common (≥1/100, <1/10): anorexia, weight decreased
Not known (cannot be estimated from the available data): hypoglycemia, hyponatremia, dehydration.

Vascular disorders
Common (≥1/100, <1/10): hot flushes
Not known (cannot be estimated from the available data): flushing.

Blood and lymphatic system disorders
Not known (cannot be estimated from the available data): anemia, thrombocytopenia, blood amylase increased, blood creatinine increased blood potassium abnormal, gamma glutamyltransferase increased.

Reproductive system and breast disorders
Not known (cannot be estimated from the available data): erectile dysfunction, sexual dysfunction.

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, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, bradycardia, hypotension, central nervous system depression, and death.
Unexpected effect of overdose: serotonin syndrome has been reported in a context of overdose or abuse with tramadol.
Death due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. The risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol and other CNS depressants, including other opioids.

Treatment
In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patient airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
~~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.~~
While naloxone will reverse some (but not all) symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice.
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.

5.2 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. To date, no clinically significant interactions have been observed. 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.

…
The format of this leaflet was determined by the Ministry of health (MOH) and its content was checked and approved by the MOH in ~~February 2011~~ 08.2012.