TopseaTramadol Capsules 100 mg

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

Topsea Tramadol Capsules 100 mg

2. Qualitative and Quantitative Composition

Each Hard Gelatin Capsule Contains:

Tramadol Hydrochloride BP 100 mg

Excipient Q.S.

3. Pharmaceutical Form

Capsules

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Dosage and Administration

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

Unless otherwise prescribed, Tramadol should be administered as follows:

Adults and children aged 12 years and over

Oral administration

Acute pain: An initial dose is 50-100 mg depending on the intensity of pain. This can be followed by doses of 50 or 100 mg 4-6 hours later, and duration of therapy should be matched to clinical need. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Pain associated with chronic conditions: Use an initial dose of 50 mg and then titrate dose according to pain severity. The initial dose may be followed if necessary by 50-100 mg every 4-6 hours. The recommended doses are intended as a guideline. Patients should always receive the lowest dose that provides effective pain control. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported.

4.3 Contraindications

The capsules are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.

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

Children

Tramadol capsules are not suitable for children below the age of 12 years.

Geriatric patients

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

Renal insufficiency/Dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency tramadol are not recommended.

4.4 Special warning and special precaution for use

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

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, or if the recommended dosage is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations.

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

Tolerance, psychic and physical dependence may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with Tramadol should only be carried out for short periods under strict medical supervision.

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.

Tramadol should be used with caution in patients with impaired hepatic and renal function.

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>.

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.

4.5 Interaction with other medicinal products and form of interaction

Tramadol should not be combined with MAO inhibitors.

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 tramadol.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects.

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.

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

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering

medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions

• Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed: Spontaneous clonus

• Inducible or ocular clonus with agitation or diaphoresis

• Tremor and hyperrflexia

• Hypertonia and body temperature > 38°C 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.

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 medicinal products known to inhibit CYP3A4, such as ketoconazole, ritonavir and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.

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.

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 duration of concomitant use should be limited.

4.6 Pregnancy and lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore, tramadol should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In new-born infants it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

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.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8 Undesirable effects

The undesirable effects are classified into system organ classes and their frequency is classified as follows: Very common (^{3}1/10), common (^{3}1/100 to <1/10), uncommon (^{3}1/1,000 to <1/100), rare (^{3}1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

Psychiatric disorders

Rare: Hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic side-effects may occur following administration of tramadol, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (mostly reduced, occasionally increased) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.

Nervous system disorders

Very common: Dizziness.

Common: Headache, somnolence.

Rare: Changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, abnormal coordination, involuntary muscle contractions, syncope.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold.

Not known: speech disorders

Eye disorders

Rare: Blurred vision.

Cardiac disorders

Uncommon: Cardiovascular regulation (palpitations, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially in connection with intravenous administration and if the patient is experiencing physical stress.

Rare: Bradycardia, increased blood pressure.

Metabolism and nutrition disorders

Not known: hypoglycaemia

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

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

Gastrointestinal disorders

Very common: Nausea.

Common: Vomiting, constipation, dry mouth.

Uncommon: Retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Frequency not known: In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

Common: Sweating.

Uncommon: Dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders

Rare: Motorial weakness.

Renal and urinary disorders

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

General disorders

Common: fatigue

Rare: Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, derealization, paranoia).

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The stomach is to be emptied by vomiting (conscious patient) or gastric irrigation. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other opioids, ATC code: N02AX02.

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also, gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

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.

5.2 Pharmacokinetic properties

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity (V d,ß = 203 + 40 l). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its Odesmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life t1/2,ß is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the Odemethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life t1/2,ß (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 + 4.9 h (tramadol) and 18.5 + 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 + 3.2 h and 16.9 + 3 h, in an extreme case 19.5 h and 43.2 h respectively.

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

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

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 Studies

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

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, nonsignificant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6.0 PHARMACEUTICAL EXCIPIENTS

6.1 List of excipients

1. Lactose BP
2. Starch BP
3. Talcum BP
4. Empty Hard Gelatin Capsules Size “2”

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

TopseaTramadol Capsules 100 mg

6.4 Special precaution for storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature contents of container

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Instruction for use handling and disposal

Keep out of reach of children.

7. Manufacturer name

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8. Marketing Authority

TOPSEA STANDARD PHARM. CO. LTD