Tramadol HCl

TRACIDOL

Prolonged Release Capsule 100mg

OPIOID ANALGESIC

Active Ingredient:
Each Tracidol Prolonged Release Capsule 100mg contains:
Tramadol Hydrochloride 100mg

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetic):
Tramadol is a centrally acting analgesic. Tramadol is a non – selective, pure agonist in the μ, and K opiate receptors, and it attaches itself most effectively to the μ-receptor. Other factors that contribute to its analgesic effects are inhibition of neuronal re-uptake of noradrenaline and enhancement of 5-HT release.
Tramadol has an antitussive effect. In opposition to morphine, analgesic doses of tramadol do not produce respiratory depression during a wide interval. Tramadol does not affect to gastrointestinal motility and its effects on the cardiovascular system are mild. The potency of tramadol is 1/10- 1/6 of that of the morphine.
Antinociceptive efficacy of TRACIDOL has been shown with osteoarthritis patients.

Absorption
Tramadol is absorbed almost completely when administered orally, and the absolute efficiency is approximately 70 %. Tramadol metabolises into O-desmethyltramadol, which has proven to have an analgesic effect in rodents. The half-life elimination of Tramadol is approximately 6 hours. The half-life increases, however, to 9 hours with the capsules of TRACIDOL due to the long absorption time.
When a single capsule of 200 mg of TRACIDOL was given to a fasting patient, the average maximum content concentration of the plasma (Cmax) achieved was 299.59 ng.ml-1 (in the interval 240 - 300ng/ml). A median Tmax 9.59 hours (9 - 12 hours) was related to this. After the dosage had been adapted, the efficiency of Tramadol produced by a capsule of TRACIDOL of 200 mg was complete, in comparison with 50 mg of immediately liberated Tramadol. In the presence of food, the availability and controlled release properties of TRACIDOL capsules were maintained, with no evidence of dose dumping. In addition, a steady state study has shown that the capsule of 200 mg of TRACIDOL has a comprehensive systemic predisposition that corresponds to an immediately absorbed product, (immediate release capsule 50 mg). The scatter of the patients participating in the study was not superior to that of the reference group.

Distribution
Tramadol has a high tissue affinity with an apparent volume of distribution of 203 ± 40 litres after oral dosing in healthy volunteers. Protein binding is limited to 20%.

Biotransformation
In humans, tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2-4. Its half-life ½b (6 healthy volunteers) is 7.9 h (range 5.4-9.6 h) and is approximately that of tramadol. The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. The clinical consequences of any such interactions are not known.

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

Linearity/non-linearity
Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. A single dose-proportionality study has confirmed a linear pharmacokinetic response (in relation to tramadol and O-desmethyltramadol) following administration of the 100 mg, 150 mg and 200 mg capsules.
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.

Indication(s):
Treatment of moderate to severe pain.

Dosage and Administration(s):
TRACIDOL capsules should be administered every 24 hours. The capsules should be swallowed whole without chewing.The dosage of Tramadol is determined by the severity of the pain and according to the clinical response of the individual patient. This is valid for all pain relief medicinal products. The correct individual dosage is one that relieves the pain for 24 hours without having any side effects or having side effects of a tolerable level. Patients switched from immediate release tramadol preparations should have their total daily dose calculated, and start on the nearest dose. It is recommended that patients are slowly titrated to higher doses to minimise transient side effects.TRACIDOL should under no circumstances be administered for longer than is strictly necessary. If repeated use or long-term treatment with tramadol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

The daily total dosage must not exceed 400 mg, unless clinical exceptional circumstances require this.

Adults and adolescents (12 years and older)
The usual starting dosage is one capsule of 100-200 mg per day. If this dosage does not relieve the pain, the dosage is to be raised until an effect of pain relief has been attained.
Tramadol is not approved for use in patients below 12 years old.

Dosing in special patients groups:
Elderly people
Patients under 75 years of age with normal liver and kidney functions can be given the normal dosage for adults. In patients over 75 years of age the half-life of Tramadol is prolonged. For those patients, an adjustment of the dosage may be required. If the dosage is increased the condition of the patient must be closely monitored.

Patients with renal insufficiency
The elimination of Tramadol may be delayed. Tramadol is not recommended for patients suffering from moderate to severe kidney insufficiency (creatinine clearance <30 ml/min).

Patients with hepatic insufficiency
Tramadol is contraindicated in patients with severe hepatic insufficiency. In patients with moderate hepatic insufficiency, tramadol is not recommended.

Paediatric population
The safety and efficacy of Tramadol has not been studied in the paediatric population. Therefore, use of Tramadol is not recommended in patients under 12 years of age.

Mode of Administration:
Oral administration.

Contraindication(s):
Tramadol Hydrochloride is contraindicated in:
1. Hypersensitivity to Tramadol or to any of the excipients of the medicinal product.
2. Acute intoxication with alcohol, hypnotics drugs, centrally acting analgesics, opioids or psychotropic drugs.
3. Tramadol should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
4. Severe hepatic insufficiency
5. Epilepsy not controlled by treatment
6. Breast-feeding, if long term treatment is necessary
7. Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
8. Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

Precaution(s) / Warning(s):
Warnings
1. In severe respiratory insufficiency, tramadol is not recommended.
2. Tramadol is not recommended in patients with moderate and severe renal insufficiency and in patients with moderate hepatic insufficiency.
3. Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.
4. Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with tramadol only if there are compelling circumstances. 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 dose limit.
5. Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended.
6. Paediatric population: The safety and efficacy of TRACIDOL has not been studied in paediatric population. Therefore, use of TRACIDOL is not recommended in patients under 12 years of age.
7. *Risk from Concomitant Use with Benzodiazepines*: Profound sedation, respiratory depression, coma, and death may result from the concomitant use of tramadol with benzodiazepines. Observational studies have demonstrated that concomitant use of opiods and benzodiazepines increases the risk of drug-related mortality compared to use of opiods alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.If the decision is made to newly prescribe a benzodiazepine and an opiod together, prescribe the lower effective dosages and minimum durations of concomitant use.If the decision is made to prescribe a benzodiazepine in a patient already receiving an opiod, prescribe a lower initial dose of benzodiapine than indicated in the absence on an opiod, and titrate based on clinical response.If the decision is made to prescribe an opiod in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opiod, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when tramadol is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opiod abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines.

Precaution for use
1. Tramadol should be used with caution in opioid-dependent patients, or in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problem affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.
2. At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods under strict medical supervision.
3. Symptoms of withdrawal reactions, similar to those during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.
4. At recommended doses tramadol is unlikely to produce clinically relevant respiratory depression. Care should however be taken when administering tramadol to patients with existing respiratory depression or excessive bronchial secretion and in those patients taking concomitant CNS depressant drugs.
5. Respiratory depression: Administer TRACIDOL cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of TRACIDOL may decrease respiratory drive to the point of apnea. In these patients, alternative non-opiod analgesics should be considered. When large doses of tramadol are administered with anaesthetic 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.
6. Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism: Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opiod metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5-1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.
7. *Serotonin Syndrome with Concomitant Use of Serotonergic Drugs*: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Tramadol with serotonergic drugs. This may occur within the recommended dosage range. Serotonin syndrome symptoms 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, diarrhoea) and can be fatal. The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Tramadol if serotonin syndrome is suspected.
8. *Adrenal Insufficiency*: Cases of adrenal insufficiency have been reported with opiod use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opiods may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

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260mm

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220mm

260 x 220

9. *Sexual Function / Reproduction*: Long term use of opioids may be associated with decreased sex hormone and levels and symptoms such as low libido, erectile dysfunction or infertility.

Effects on Ability to Drive and Use Machines
Tramadol may cause drowsiness. Alcohol and other medicinal products, which depress the central nervous system, may increase this effect. If affected, the patient should not drive or operate machinery.

Interaction with Other Medicaments:
Concomitant use is contraindicated with:
Non-selective MAO inhibitors
Risk of serotoninergic syndrome: diarrheoea, tachycardia, sweating, tremor, confusion, even coma.
Selective MAO-A inhibitors
Extrapolation from non-selective MAO inhibitors:
Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, tremor, confusion, even coma.
Selective MAO-B inhibitors
Central excitation, symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, tremor, confusion, even coma. In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol.
Concomitant use is not recommended with:
Alcohol
Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. Avoid intake of alcohol drinks and medicinal products containing alcohol.
Carbamazepine and other enzyme inducers
Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.
Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)
Decrease of the analgesic effect by blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.
Concomitant use which needs to be taken into consideration:
1. Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates. Increased risk of respiratory depression which can be fatal in cases of overdose.
2. Other depressants of central nervous system, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen. These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
3. *Benzodiazepines*: Due to additive pharmacologic effect, the concomitant use of opiods with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opiods and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opiods interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opiods and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opiod-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients whom alternative treatment options are inadequate. Limit dosage and duration of concomitant use of benzodiazepines and opiods, and follow patients closely for respiratory depression and sedation
4. As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol and warfarin like compounds are administered concurrently due to reports of increase INR.
5. Other drugs 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.
6. Medicinal products reducing the seizure threshold, such as bupropion, serotonin re-uptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics concomitant use of tramadol with these drugs can increase the risk of convulsions.
7. *Serotonergic Drugs*: The concomitant use of opiods with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe patient, particularly during treatment initiation and dose adjustment. Discontinue Tramadol if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Pregnancy and Lactation:
Pregnancy
Tramadol has been shown to cross the palcenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. TRACIDOL is not recommended for pregnant women.
Lactation
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 400mg, 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.

Side Effect(s):
The most commonly reported undesirable effects caused by the medicinal product are nausea and dizziness, which both appear in over 10% of the patients.
Disorders of the digestive system
Very common (> 10%) : nausea
Common (1-10%) : emesis, constipation, drying of the mouth
Uncommon (< 1%) : vomiting, irritation of the digestive system (sense of pressure in the stomach, bloating)
Rare (<0.1%) : change in appetite
Disorders in connection with the heart and arteries
Uncommon (< 1%) : cardiovascular regulation (palpitation, tachycardia, hypo tension in connection with posture or cardiovascular collapse). These undesirable effects may be found especially in patients who are physically over-strained.
Rare (< 0.1 %) : bradycardia, increase in blood pressure
Disorders of the central and peripheral nervous system
Very common (> 10%) : dizziness
Common (1-10%) : headache, incoherence
Rare (< 0.1%) : respiratory depression. If the recommended dosages are considerably exceeded and simultaneously given with other compounds that affect the central nervous system, a respiratory depression may occur. Seizures resembling epilepsy occurred mainly after large doses of Tramadol had been administered or when the patient had been simultaneously treated with medicinal products which may reduce the seizure threshold, or, as such, cause cerebral convulsions, numbness, trembling, and changes in appetite.

Psychiatric disorders
Rare (< 0.1%) : psychic side effects may occur after the administration of Tramadol and there may occur individual variations of the strength and the character of the adverse effects (depending on the personality and the duration of the medication). Changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, sporadically increases) and changes in the cognitive and sensory capabilities (for example decision making, disorders of perception), hallucinations, confusion, sleep disturbances and nightmares.
Very rare (< 0.01%) : addiction, abuse and withdrawal symptoms may occur. Withdrawal symptoms may be: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremors and disorders of the digestive system.
The majority of these are very similar to those occurring in connection with opiate withdrawal.
Visual disorders
Rare (< 0.1%) : blurred vision
Respiratory disorders
Rare (< 0.1%) : dyspnoea and wheezing.
Exacerbation of asthma has also been reported, although the causality has not been established.
Skin and appendages disorders
Common (1-10%) : sweating
Uncommon (< 1%) : skin reactions (for example itching, rash, urticaria)
Musculo-Skeletal system disorders
Rare (< 0.1%) : motor weakness
Liver and biliary system disorders
In a few isolated cases an increase in liver enzymes has been reported in connection with a temporary therapeutic use of Tramadol.
Urinary system disorders
Rare (< 0.1%) : urinary disorders (difficulties in passing urine and urinary retention)
Body as whole
Rare (< 0.1%) : allergic reactions (for example dyspnoea, bronchospasms, wheezing, angioneurotic oedema and anaphylaxis).
In postmarketing experience, there were reported cases such as follows:
- Serotonin syndrome
- Adrenal insufficiency
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opiods in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.
- Infertility: Chronic use of opioids may cuase reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms of Overdose
Also for other opioid analgesics, the typical symptoms of overdose are miosis, emesis, cardiovascular collapse, sedation and coma, seizures and respiratory depression.
Treatment of Overdose
Supportive action should be taken: the respiratory tract should be kept open and the cardiovascular functions should be supported. In case of respiratory depression, naloxone may be used in resuscitation. The convulsions can be controlled with diazepam.
Tramadol is minimally eliminated from the serum via haemodialysis or blood filtering. For this reason, it is not sufficient to perform only haemodialysis or blood filtering for the treatment of acute Tramadol intoxication.
The removal of the unabsorbed drug by gastric emptying is useful; particularly when a modified release formulation has been taken.

Storage Condition(s):
Store at temperature below 30°C

Shelf-Life:
2 years.

Product Description & pack Size(s):
100mg: Hard gelatine size 1 capsules with a light blue cap and body containing white pellets.
Blister of 10's x 3 (30's); 10's x 50 (500's); 10's x 100 (1000's) / box

Y. S. P.®

Manufacturer:
SMB Technology S.A.,
Rue du Parc Industriel 39,
6900 Marche-en-Famenne,Belgium.

Importer & Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. **(192593 U)**
Lot 3, 5 & 7, Jln. P/7, Sec. 13,
Kaw. Perindustrian Bdr. Baru Bangi,
43000 Kajang, Selangor D. E., Malaysia.

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