TRACIDOL® CAPSULE 50MG

Ingredient(s):
Each capsule contains:
Tramadol Hydrochloride 50mg

Pharmacology:
Pharmacodynamic:
Tramadol is a centrally acting opioid analgesic. It is a nonselective pure agonist at μ, δ and κ opioid receptors with a higher affinity for μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal re-uptake 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 not affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 to 1/6 that of morphine.

Pharmacokinetics:
The absorption of tramadol following oral administration is rapid and almost complete. The rate or extent of absorption is not significantly affected by administration with food.

Tramadol is widely distributed, crosses the placental and blood-brain barriers, and appears in small amounts in the breast milk.

Tramadol is subject to first-pass metabolism and is metabolized by N- and O-demethylation and glucuronidation or sulphation in the liver. The metabolite O-desmethyltramadol is pharmacologically active and is more potent than the parent substance by the factor 2-4. Its half-life is approximately 7.9 hours.

The elimination half-life of tramadol is about 6 hours irrespective of the mode of administration. In patients more than 75 years of age, it may be prolonged by a factor of approximately 1.4.

Tramadol is secreted mainly in the urine predominantly as metabolites. In cases of impaired hepatic and renal function the half-life may be slightly prolonged.

Indication(s):
For the management of moderate to severe pain.

Dosage and Administration:
The dosage should be adjusted to the intensity of pain and the individual's response to the analgesic action of tramadol.
Adults and adolescents > 12 years old:
50 – 100mg (1 – 2 capsules) every six hours as needed.
An initial dose of 50mg is usually more effective for moderate pain whereas an initial dose of 100mg is usually more effective for more severe pain.
Tramadol is not approved for use in patients below 12 years old.

Maximum daily dose:
400mg, except in special clinical circumstances.

Geriatric patients:
The usual dosages may be used except in patients above the age of 75 years, a downward adjustment of the dose and/or prolongation of the dosage interval are recommended.
Hepatic and renal insufficiency/dialysis:
In acute pain, a dosage adjustment is not necessary as Tramadol is given only once or a few times. In patients with severe renal and/or hepatic insufficiency, Tramadol should not be administered. In less severe cases, prolongation of the dosage interval is recommended.

Peadiatric 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.

Route of Administration:
To be taken orally.

Contraindication(s):
1. Known hypersensitivity towards tramadol or any of the excipients.
2. Acute intoxication with alcohol, hypnotics, analgesics, opioids, and psychotropics.
3. Patients who are receiving MAO inhibitors or have taken them within the last 14 days.
4. Tramadol must not be used for narcotic withdrawal treatment.
5. Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
6. 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):
1. Tramadol must be used with special care in opioid dependence, reduced level of consciousness of unclear origin, disorders of the respiratory centre or function, and increased intracranial pressure.
2. Tramadol should be used with care in patients with increased reactivity to opioids. Patients known to suffer from convulsions should be carefully monitored during treatment.
3. Tramadol has a low dependence potential. On long-term use, tolerance, psychic and physical dependence may develop. Therefore, in patients with a tendency towards drug abuse or dependence, treatment should only be carried out for short periods under strict medical supervision.
4. Tramadol is a potent drug for the relief of pain and therefore should not be used in minor pain.
5. Tramadol may affect or impair the ability to drive or operate machinery, particularly when used in conjunction with other psychotropic medicines or alcohol.
6. Tramadol is not suitable as a substitute in opioid-dependent patients. Although tramadol is an opiate agonist, it cannot suppress morphine withdrawal symptoms.
7. *Paediatric population:* The safety and efficacy of tramadol has not been studies in the paediatric population. Therefore, use of tramadol is not recommended in patients under 12 years of age.
8. Respiratory depression: Administer tramadol 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 tramadol may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid 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.
9. *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 opiod-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 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.
10. *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 onclinical 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.
11. *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.

12. *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.
13. *Sexual Function / Reproduction:* Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction or infertility.

Interaction with Other Medicaments:
1. On premedication with MAO inhibitors in the last 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system and respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors and Tramadol cannot be excluded.
2. Concomitant administration with other centrally depressant substances including alcohol may potentiate the CNS effects.
3. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.
4. 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.
5. Tramadol may induce convulsions and increase the potential of selective serotonin re-uptake inhibitors, tricyclic antidepressants, neuroleptics and other seizure threshold lowering drugs to cause convulsions.
6. Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (O-demethylation) possibly also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.
7. 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.
8. *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 placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. Tramadol 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) / Adverse Reaction(s):
Frequently: nausea and dizziness.
Occasionally: vomiting, constipation, sweating, dry mouth, headache, and muzziness.
Rarely: palpitation, tachycardia, postural hypotension or cardiovascular collapse; gastrointestinal irritation; dermal reactions (e.g. pruritus, rash, urticaria); respiratory depression.
Very rarely: motorial weakness; changes in appetite; blurred vision; micturition disorders (difficulty in passing urine and urinary retention); various psychic side-effects including changes in mood and activity as well as changes in cognitive and sensorial capacity which vary individually in intensity and nature (depending on personality and duration of medication); allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; worsening of asthma; epileptiform convulsions; increase in blood pressure and bradycardia; respiratory depression especially when recommended doses are exceeded and other centrally depressants are administered concomitantly.
Dependence may develop. Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.
In a few isolated cases, an increase in liver enzyme values has been reported.
In postmarketing experience, there were reported cases such as follows:
- Serotonin syndrome (See Warnings and Precautions)
- Adrenal insufficiency (See Warnings and Precautions)
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-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: In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected, in particular miosis, vomiting, cardiovascular collapse, reduced level of consciousness up to coma, convulsions and respiratory depression up to respiratory arrest.
Treatment: The general emergency measures to keep open the respiratory tract (aspiration), maintenance of respiration and circulation depending on the symptoms apply. The stomach is to be emptied by the induction of vomiting (conscious patient) or rinsed. An antidote for respiratory depression is naloxone. In animal studies, naloxone had no effect on convulsions. In such cases, diazepam should be given IV.

Storage Condition(s):
Store at temperature below 30°C. Protect from light and moisture.

Shelf-Life:
3 years from the date of manufacture.

Product Description & Packing(s):
A #4 yellow body, green cap hard gelatin capsule containing white powder.
Blister packing of 10's x 10 and 10's x 50.

Y. S. P.®
Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
Lot 3, 5, 7, 12 & 14, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor, Malaysia.
Ordering Line: 1 800 88 3027
Product Info: 1 800 88 3679

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