

Jysk

(Tramadol HCl Ph. Eur.)

جسک

(ٹراماڈول ہائیڈروکلورائیڈ پی ایچ ای یو آر)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; HEPATOTOXICITY; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS.

Addiction, Abuse, and Misuse: Tramadol exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing tramadol, and monitor all patients regularly for the development of these behaviors and conditions.

Life-Threatening Respiratory Depression: Serious, life-threatening, or fatal respiratory depression may occur with use of tramadol. Monitor for respiratory depression, especially during initiation of tramadol or following a dose increase.

Accidental Ingestion: Accidental ingestion of even one dose of tramadol, especially by children, can result in a fatal overdose of tramadol.

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-Threatening Respiratory Depression in Children: Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases occurred following tonsillectomy and/or adenoidectomy, and in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. Tramadol is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the use of tramadol in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of tramadol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes: The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.

Hepatotoxicity: Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants: Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of tramadol and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

COMPOSITION

Each **Jysk** 50mg capsule contains 50mg Tramadol Hydrochloride.

DESCRIPTION

Tramadol is a centrally acting synthetic opioid analgesic.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of Tramadol. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

In contrast to morphine, Tramadol has not been shown to cause histamine release. At therapeutic doses, Tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Absorption: The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic Tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults.

Food Effects: Oral administration of Tramadol with food does not significantly affect its rate or extent of absorption, therefore, Tramadol can be administered without regard to food.

Distribution: The binding of Tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism: Tramadol is extensively metabolized after oral administration by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as extractable metabolites.

Elimination: Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic Tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic Tramadol increased from approximately six hours to seven hours upon multiple dosing.

Pharmacodynamics: Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to µ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to µ-opioid receptors. In animal models, M1 is up to 6 times more potent than Tramadol in producing analgesia and 200 times more potent in µ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both Tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

INDICATIONS

Cap. **Jysk** is indicated for the management of moderate to moderately severe pain.

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

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. 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 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 is not recommended.

DRUG INTERACTIONS

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.

Serotonergic Drugs: There have been post marketing reports of serotonin syndrome with use of Tramadol and SSRIs/SNRIs or MAOIs and α2-adrenergic blockers. Caution is advised when Tramadol 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 Tramadol 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.

Use with Carbamazepine: Patients taking carbamazepine may have a significantly reduced analgesic effect of Tramadol. Because carbamazepine increases Tramadol metabolism and because of the seizure risk associated with Tramadol, concomitant administration of Tramadol and carbamazepine is not recommended.

Use with Quinidine: Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and Tramadol results in increased concentrations of Tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that Tramadol has no effect on quinidine metabolism.

Potential for Other Drugs to Affect Tramadol: In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of Tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with Tramadol may affect the metabolism of Tramadol leading to altered Tramadol exposure.

Potential for Tramadol to Affect Other Drugs: In vitro studies indicate that Tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when Tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use with Cimetidine: Concomitant administration of Tramadol with cimetidine does not result in clinically significant changes in Tramadol pharmacokinetics. Therefore, no alteration of the Tramadol dosage regimen is recommended.

Use with Digoxin and Warfarin: Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

Pregnancy, Teratogenic Effects: Pregnancy Category C

Tramadol has been shown to be embryo toxic and fetotoxic in mice.

SIDE EFFECTS

Incidence of Treatment-Emergent Adverse Events (≥2.0%)

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Gastrointestinal: Abdominal pain, Anorexia, Flatulence.

Musculoskeletal: Hypertonia.

Skin: Rash.

Special Senses: Visual disturbance.

Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Other events which have been reported with the use of Tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure, and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures, and coma) has been reported with Tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

PRECAUTIONS

Acute Abdominal Conditions: The administration of Tramadol may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal and Hepatic Disease: Dose reduction is recommended.

Use in Special Populations

Renal: Impaired renal function results in a decreased rate and extent of excretion of Tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended. The total amount of Tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic: Metabolism of Tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for Tramadol and longer Tramadol and M1 elimination half-lives (13 hrs. for Tramadol and 19 hrs. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended.

Geriatric: Healthy elderly subjects aged 65 to 75 years have plasma Tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years.

OVERDOSE

Acute overdosage with Tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death. Deaths due to overdose have been reported with abuse and misuse of Tramadol. Review of case reports has indicated that the risk of fatal overdose is further increased when Tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of Tramadol overdosage, primary attention should be given to the reestablishment of a patent 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.

CONTRAINDICATIONS

Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to Tramadol, any other component of this product or opioids.

Tramadol is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients.

PRESENTATION

Jysk 50mg Capsule: 1x10's/pack

DOSAGE

As directed by the physician.

INSTRUCTIONS

Store below 30°C.

Protect from sunlight and moisture.

Keep out of reach of children.

Detailed prescribing information is available on request.

Manufactured by:
AsianContinental (Pvt.) Ltd.
D-32, S.I.T.E. II, Super Highway,
Karachi-Pakistan.



An ISO Certified Company

LF7/054/00

خوراک:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو 30°C سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔