

ABRIDGED PRESCRIBING INFORMATION FOR MEDICAL PROFESSIONALS

Jysk-P

(Tramadol HCl 37.5mg
+Paracetamol 325mg)

Jysk-P Forte

(Tramadol HCl 75mg
+Paracetamol 650mg)

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 Hydrochloride/Paracetamol 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 Hydrochloride/Paracetamol tablet, 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. Monitor for respiratory depression, especially during initiation of or following a dose increase.

Accidental Ingestion: Accidental ingestion of even one dose, 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 Hydrochloride/Paracetamol 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 Hydrochloride/Paracetamol 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: Prolong use 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 Hydrochloride/Paracetamol requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.

Hepatotoxicity: Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol containing product.

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 Hydrochloride/Paracetamol 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-P** Tablet contains 37.5 mg Tramadol Hydrochloride and 325 mg Paracetamol.
Each **Jysk-P Forte** Tablet contains 75 mg Tramadol Hydrochloride and 650 mg Paracetamol.

MODE OF ACTION

Tramadol is a centrally acting synthetic opioid analgesic. 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 reuptake 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. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol to human analgesia is dependent upon the plasma concentrations of each compound.

DESCRIPTION

Tramadol is a centrally acting synthetic opioid analgesic, paracetamol is a non-opiate, non-salicylate analgesic.

CLINICAL PHARMACOLOGY

Absorption: The absolute bioavailability of tramadol from tablets has not been determined. Tramadol Hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tablets. The mean peak plasma concentration of racemic tramadol after administration of two tablets occurs at approximately two and three hours, respectively, post-dose. Peak plasma concentrations of paracetamol occur within one hour and are not affected by co-administration with tramadol. Oral absorption of paracetamol following administration occurs primarily in the small intestine.

Food Effects: When Tramadol Hydrochloride/Paracetamol was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for paracetamol. However, peak plasma concentrations, and the extents of absorption, of tramadol and paracetamol were not affected. The clinical significance of this difference is unknown.

Metabolism: Following oral administration, tramadol is extensively metabolized 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.

Elimination: Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol are approximately 5-6 and 7 hours, respectively, after administration of tablet. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of tablet. The half-life of paracetamol is about 2 to 3 hours in adults. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner.

INDICATIONS

Acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

DOSAGE AND ADMINISTRATION

Adults and Adolescents (ages 12 and over)

- Indicated for short-term use of five days or less.
 - Do not exceed the recommended dose.
 - Do not co-administer with other Tramadol or Paracetamol containing products.
 - Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
 - In circumstances where physical dependence is possible, use a gradual downward taper and do not stop use abruptly.
 - Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.
- Jysk-P:** 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.
Jysk-P Forte: 1 tablet 6 hourly as needed for pain relief up to a maximum of 4 tablets per day.

Renal insufficiency:

In patients with renal 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.
For patients with creatinine clearance < 30 mL/min, the dosing interval of:

- **Jysk-P** not to exceed 2 tablets every 12 hours.
- **Jysk-P Forte** not to exceed 1 tablet every 12 hours.

Hepatic impairment:

The use of Tramadol Hydrochloride/Paracetamol in patients with hepatic impairment is not recommended.

SIDE EFFECTS

Tramadol: Postural hypotension, bradycardia, collapse. Post-marketing surveillance of Tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.

Paracetamol: Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

The most commonly reported undesirable effects during the clinical trials performed with the Tramadol/Paracetamol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients. CNS depression, severe hypotension (including orthostatic hypotension and syncope), seizures, sleep-related breathing disorders (e.g. central sleep apnoea, sleep-related hypo-oxygenaemia); reversible adrenal insufficiency, spasm of sphincter of Oddi, decreased bowel motility particularly in post-operative patients; drug tolerance, misuse, abuse, or addiction; withdrawal symptoms. Rarely, hyponatraemia.

Gastrointestinal disorders: Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence.

Metabolism and nutrition disorders: Anorexia.

Nervous system disorders: Dizziness, somnolence, headache, trembling.

Psychiatric disorders: Confusional state, altered mood, anxiety, nervousness, euphoric mood, sleep disorders, insomnia.

Skin and subcutaneous tissue disorders: Hyperhidrosis, pruritus.

Potentially Fatal: Acute liver failure, respiratory depression, serotonin syndrome; neonatal withdrawal syndrome (long-term use during pregnancy). Rarely, serious anaphylactoid reactions and serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis).

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 postmarketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and 2-adrenergic blockers. Caution is advised when Tramadol Hydrochloride/Paracetamol is co-administered 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 Hydrochloride/Paracetamol 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.

Triptans: If concomitant treatment of Tramadol Hydrochloride/Paracetamol with a triptan 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 Hydrochloride/Paracetamol and carbamazepine is not recommended.

Opioid agonists-antagonists: Concomitant use of nalbuphine, buprenorphine, pentazocine 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.

WARNINGS AND PRECAUTIONS

In severe respiratory insufficiency, Tramadol Hydrochloride/Paracetamol is not recommended. Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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 this medicine only if there are compelling circumstances. Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Pediatric Use: The safety and effectiveness has not been studied in the pediatric population. Because of the risk of life-threatening respiratory depression and death.

Tramadol Hydrochloride/Paracetamol is contraindicated for all children younger than age 12 years of age. Tramadol Hydrochloride/Paracetamol is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy.

Avoid the use of Tramadol Hydrochloride/Paracetamol 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 unless the benefits outweigh the risks.

Geriatric Use: In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease; and multiple drug therapy.

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

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Tramadol Hydrochloride/Paracetamol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Tramadol Hydrochloride/Paracetamol 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.

OVERDOSE

Tramadol Hydrochloride/Paracetamol is a combination product. The clinical presentation of overdose may include the signs and symptoms of Tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol over dosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. Emergency treatment: Maintain respiratory and circulatory functions. A blood sample should be taken as soon as possible in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests. Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks. Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage. Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam. Treatment of acute intoxication with Tramadol Hydrochloride/Paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

CONTRAINDICATIONS

Tramadol Hydrochloride/Paracetamol is contraindicated for: All children younger than 12 years of age. Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Tramadol Hydrochloride/Paracetamol is also contraindicated in patients with: Significant respiratory depression. Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment. Patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Previous hypersensitivity to tramadol, paracetamol, any other component of this product, or opioids. Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days.

PRESENTATION

Jysk-P Tablets : 1 x 10's/pack
Jysk-P Forte Tablets : 1 x 10's/pack

DOSAGE

As directed by the physician.

INSTRUCTIONS

Store below 30°C.

Do not take with any medicine that contains paracetamol.

Protect from sunlight and moisture.

Keep out of reach of children.

Detailed prescribing information is available on request.



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