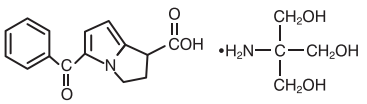
KTR
(Ketorolac Tromethamine)

30mg /ml
Injection U.S.P.
for I.M. / I.V. use only

DESCRIPTION: KTR (ketorolac tromethamine) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41.
Its molecular formula is $C_{19}H_{24}N_2O_6$ and the chemical structure is:



The sterile solution is clear and light yellow in colour.

COMPOSITION:
Each ml contains: Ketorolac Tromethamine U.S.P. 30mg
Properties and effects: Ketor is a potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). Its mode of action is to inhibit the cyclooxygenase enzyme system and hence prostaglandin synthesis and it demonstrates a minimal anti-inflammatory effect at its analgesic dose. KTR is not an anesthetic agent and possesses no sedative or anxiolytic properties; therefore it is not recommended as a pre-operative medication for the support of anesthesia when these effects are required. It is not an opioid and, has no known effects on opioid receptors. **Pharmacokinetics:** Following intramuscular administration, ketorolac tromethamine was rapidly and completely absorbed, a mean peak plasma concentration of 2.2 pg/m1 occurring an average of 50 minutes after a single 30 mg dose. The influences of age, kidney and liver function on terminal plasma half-life and mean total, clearance are outlined in the table below (estimated from a single 30mg i.m. dose of ketorolac tromethamine). Intravenous administration of a single 10mg dose of ketorolac tromethamine resulted in a mean peak plasma concentration of 2.4 pg/ml occurring an average of 5.4 minutes after dosing, with an average terminal plasma elimination halt-life of 5.1 hours, an average volume of distribution of 0.15 1/kg, and a total plasma clearance of 0.35 ml/min/kg. The pharmacokinetics of ketorolac tromethamine in man following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every 6 hours for one day. No changes in clearance occur with continued dosing. The primary route of excretion of ketorolac tromethamine and its metabolites is renal: 91.4% (mean) of a given dose being found in thQurine and 6.1./0 (mean) in the feces. More than 99% of the ketorolac tromethamine in plasma is protein-bound over a wide concentration range. **Indications:** KTR ampoules are indicated for the short-term management of moderate to severe acute postoperative pain. **Dosage and Administration:** KTR ampoules are for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over no less than 15 seconds. KTR ampoules should not be used for epidural or spinal administration. The time to onset of analgesic following both i.v. and i.m. administration is similar and is, approximately 30 minutes, with maximum analgesia occurring within 1 to 2 hours. The median duration of analgesia is generally 4 to 6 hours. Dosage should be adjusted according to the severity of the pain and the patient response. **Duration of treatment:** The administration of continuous multiple daily doses of KTR intramuscularly or intravenously should not exceed 2 days because adverse events may increase with prolonged usage. **Adults:** the recommended initial dose of KTR is 10 mg, followed by 10-30 mg every 4 to 6 hours as required. In the initial postoperative period, KTR may be given as often as every 2 hours if needed. The lowest effective dose should be given. A total daily dose of 90 mg for non-elderly and 60 mg for the elderly, renally-impaired patients and patients less than 50 kg should not be exceeded. For patients receiving KTR ampoules, and who are converted to KTR tablets, the total combined daily dose should not exceed 90 mg (60 mg for the elderly, renally-impaired patients and patients less than 50 kg) and the oral component should not exceed 40 mg on the day the change of formulation is made. Patients converted to oral treatment as soon as possible. **Special dosage instructions Elderly patients:** For patients over 65 years, the lower end of the dosage range is recommended; a total daily dose of 60 mg should not be exceeded (see Precautions). **Children:** Safety and efficacy in children have not been established. Therefore, KTR is contraindicated for use in children under 16 years of age. **Renal impairment:** Since ketorolac tromethamine and its metabolites are excreted primarily by the kidney, KTR is contraindicated in moderate to severe renal impairment (serum creatinine > 160 prno1/1); patients with lesser renal impairment should receive a reduced dose (not exceeding 60 mg per day i.v. or i.m.), and their renal status should be closely monitored. **Contraindications** - a history of peptic ulcer or gastrointestinal bleeding - suspected or confirmed cerebrovascular bleeding - haemorrhagic diatheses, including coagulation disorders - patients with hypersensitivity to ketorolac tromethamine or other NSAIDs and patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients) - patients with the complete or partial syndrome of nasal polyps, angio-edema or bronchospasm- concurrent treatment with other NSAIDs, oxpentifylline, probenecid or lithium salts - hypovolemia from any cause, or dehydration - moderate or severe renal impairment (serum creatinine >160pmol/1) - a history of asthma - patients who have had operations with a high Ask of haemorrhage or incomplete homeostasis - patients on anticoagulants including low-dose heparin (2500-5000 units 12-hourly) - during pregnancy, labor, delivery or lactation - children under 16 years of age. **Precautions:** Physicians should be aware that in some patients pain relief may take longer than 30 minutes after i.v. or i.m. administration. **Elderly patients:** Patients over the age of 65 years may be at a greater risk of experiencing undesirable effects than younger patients. This age-related risk is common to all NSAIDs. **Gastrointestinal effects:** KTR can cause gastrointestinal irritation. Ulc bleeding in patients with or without a history of previous symptoms.
Respiratory effects: Bronchospasm may be precipitated in patients with a history of asthma. **Renal effects:** Drugs that inhibit prostaglandin biosynthesis (including NSAIDs) have been reported to cause nephrotoxicity, including but not limited to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure. In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. As with other drugs that inhibit prostaglandin synthesis, elevations of serum urea. Creatinine and potassium have been reported with KTR and may occur after one dose. **Hepatic effects:** Borderline elevations of one or more liver function tests may occur. These abnormalities may be transient, may remain unchanged, or may progress with continued therapy. **Haematological effects:** Patients with coagulation disorders should not receive KTR. Patients on anticoagulation therapy may be at increased risk of bleeding if given KTR concurrently. Ketorolac tromethamine inhibits platelet aggregation and prolongs bleeding time. In patients with normal bleeding function, bleeding times were raised, but not outside the normal range of 2 to 11 minutes. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24-48 hours after ketorolac tromethamine is discontinued. Therefore, KTR should not be used in patients who have had operations with a high risk of haemorrhage or incomplete homeostasis. **Pregnancy:** Nursing mothers the safety of KTR in human pregnancy has not been established. KTR is therefore contraindicated during pregnancy, labor or delivery. As ketorolac tromethamine has been detected in human milk at low levels, it is also contraindicated in mothers who are breast-feeding. **Undesirable effects Gastrointestinal tract:** abdominal discomfort, constipation, diarrhoea, dyspepsia, eructation, flatulence, fullness, gastritis, gastrointestinal bleeding, gastrointestinal pain, nausea, pancreatitis, peptic ulcer, perforation, stomatitis, vomiting. Central nervous/ musculoskeletal systems: abnormal dreams, abnormal taste and vision, abnormal thinking, aseptic meningitis, convulsions, depression, dizziness, drowsiness, dry mouth, euphoria, excessive thirst, functional disorders, hallucinations, headache, hearing loss, hyperkinesia, inability to concentrate, insomnia, myalgia, nervousness, paraesthesia, stimulation, sweating. Tinnitus, vertigo. Urinary tract and kidneys: acute renal failure, flank pain (with or without haematuria), glomerular nephritis, haemolytic uremic syndrome, hyperkalaemia, hyponatremia, increased urinary frequency, interstitial nephritis, nephrotic syndrome, oliguria, raised serum urea and creatinine, renal papillary necrosis. Cardiovascular/ haematological systems: bradycardia, flushing, hypertension, pallor, purpura thrombocytopenia. Respiratory system: asthma, dyspnea, pulmonary edema. **Skin:** exfoliative dermatitis, Lyell's syndrome, maculopapular rash, pruritus, Stevens-Johnson syndrome, urticaria. Hypersensitivity reactions: anaphylaxis, bronchospasm, flushing and rash, hypotension, laryngeal edema. Such reactions may occur in patients with or without known sensitivity to KTR or other NSAIDs. Bleeding: epistaxis, hematomata, postoperative wound haemorrhage. Other: abnormal liver function tests, asthenia, edema, injection site pain, weight gain. In normovolemic healthy volunteers, ketorolac tromethamine reduces the diuretic response to frusemide by approximately 20%, so particular care should be taken in patients with cardiac decompensation. There is an increased risk of renal impairment when ketorolac tromethamine is administered concurrently with ACE inhibitors, particularly in volume-depleted patients. **Overdosage:** Doses of 360 mg given intramuscularly over an 8-hour interval for 5 consecutive days have caused abdominal pain and peptic ulcers which have healed after discontinuation of dosing. Two patients recovered from unsuccessful suicide attempts. One patient experienced nausea after 210 mg KTR, and the other hyperventilation after 300mg KTR. **Special remarks Incompatibilities:** KTR ampoules should not be mixed in a small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride as precipitation of ketorolac tromethamine will occur. KTR ampoules are compatible with normal saline, 5% dextrose, Ringer's solution, Ringer- Lactate solution or Plasmalyte solution. Compatibility with other drugs is unknown. Stability this medicine must not be used after the expiry date (EXP) shown on the pack.
Instructions: Store below 30ºC.
Protect from heat & light.
Do not use if particles found in injection.
Discard any portion of the contents
remaining after use.
Keep all medicines out of the reach of children.
Presentation: KTR (Ketorolac Tromethamine)
Injection U.S.P. is available in pack of 1ml x 5 ampoules.

Manufactured for:
Daneen Pharma (Pvt.) Ltd.
27-Sundar Industrial Estate, Sundar Raiwind Road Lahore, Pakistan.
Tel: +92-42-35297781-2, **Email:** info@daneenpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.daneenpharma.com

Manufactured by:
Genix Pharma (Pvt.) Ltd.
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.genixpharma.com