06-11-2019

TEKAC® 30mg/ml Injection

(Ketorolac Tromethamine)

For I.M. / I.V. use

DESCRIPTION:

TEKAC® is a non-narcotic analgesic belonging to the non-steroidal anti-inflammatory drug (NSAID) class of medicines with analgesic, anti-inflammatory and antipyretic properties

COMPOSITION:

TEKAC® 30mg/ml Injection
Each ml contains:
Ketorolac Tromethamine USP.....30mg

CLINICAL PHARMACOLOGY:
Mechanism of Action: The mode of action of ketorolac is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis and it demonstrates a minimal anti-inflammatory effect at its analgesic dose
Pharmacodynamics: Ketorolac is neither an opioid nor an anesthetic agent. It has no known effects on opioid receptors, 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
Pharmacokinetics
Intramuscular: Following intramuscular administration, ketorolac was rapidly and completely absorbed. A mean peak plasma concentration of 2.2µg/ml occurred at an average of 50 minutes after a single 30mg dose. Age, kidney and liver function affect terminal plasma half-life and mean total clearance as outlined in the table below (estimated from a single 30mg IM dose of ketorolac)

Type of subjects	Total clearance (l/hr./kg) mean (range)	Terminal half-life (hrs.) mean (range)
Normal subjects (n=54)	0.023 (0.010 - 0.046)	5.3 (3.5 - 9.2)
Healthy elderly subjects (n=13) (mean age 72)	0.019 (0.013 - 0.034)	7.0 (4.7 - 8.6)
Patients with hepatic dysfunction (n=7)	0.029 (0.013 - 0.066)	5.4 (2.2 - 6.9)
Patients with renal impairment (n=25) (serum creatinine 160-430 micromol/l)	0.016 (0.005 - 0.043)	10.3 (5.9 - 19.2)
Renal dialysis patients (n=9)	0.016 (0.003 - 0.036)	13.6 (8.0 - 39.1)

Intravenous: Intravenous administration of a single 10mg dose of ketorolac resulted in a mean peak plasma concentration of 2.4•g/ml at an average of 5.4 minutes after dosing. The terminal plasma elimination half-life was 5.1 hours, average volume of distribution 0.15 l/kg, and total plasma clearance 0.35ml/min/kg

The pharmacokinetics of ketorolac in man following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every six hours for one day. No changes in clearance occurred with chronic dosing

Binding and Distribution: More than 99% of the ketorolac in plasma is protein-bound over a wide concentration range. Plasma protein binding is independent of concentration. Ketorolac tromethamine poorly penetrates the blood brain barrier (levels in the cerebrospinal fluid were found to be 0.002 times or less than those in plasma)

Metabolism: Ketorolac tromethamine is largely metabolized in the liver
Excretion: The primary route of excretion of ketorolac and its metabolites is renal: 91.4% (mean) of a given dose being found in the urine and 6.1% (mean) in the faeces

INDICATIONS:

TEKAC® is indicated for the short-term management of moderate to severe, post-operative pain. The total duration of ketorolac use should not exceed five days

DOSAGE AND ADMINISTRATION:
Ketorolac injection is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over at least 15 seconds. Ketorolac injection should not be used for epidural or spinal administration

The time to onset of analgesic effect following both I.V. and I.M. administration is similar and is approximately 30 minutes, maximum analgesia occurs within one to two hours. The median duration of analgesia occurring within 1 to 2 hours. Analgesia normally lasts for four to six hours

Dosage should be adjusted according to the severity of the pain and the patient's response

DURATION OF TREATMENT:
The administration of continuous multiple daily doses of ketorolac intramuscularly or intravenously should not exceed two days because adverse events may increase with prolonged usage. There has been limited experience with dosing for longer periods since the vast majority of patients have transferred to oral medication or no longer require analgesic therapy after this time

Adults: The recommended initial dose of ketorolac injection is 10mg followed by 10 to 30mg every four to six hours as required. In the initial post-operative period, ketorolac Injection may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90mg for non-elderly and 60mg for the elderly, patients with renal impairment and patients less than 50kg should not be exceeded. The maximum duration of treatment should not exceed two days

Patients receiving ketorolac injection, and who are converted to oral ketorolac, should receive a total combined daily dose not exceeding 90mg (60mg for the elderly, patients with renal impairment and patients less than 50kg). The oral component should not exceed 40mg on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible

SPECIAL DOSAGE INSTRUCTIONS:
Elderly: For patients over 65 years, the lower end of the dosage range is recommended; a total daily dose of 60mg should not be exceeded
Children: Safety and efficacy in children have not been established. Therefore, ketorolac injection is not recommended for use in children under 16 years of age
Renal impairment: Since ketorolac and its metabolites are excreted primarily by the kidney, ketorolac is contraindicated in moderate to severe renal impairment (serum creatinine >160µmol/l), patient with lesser renal impairment should receive a reduce dose (not exceeding 60mg per day I.V. or I.M.), and their renal status should be monitored
Kinetics in special clinical situations: Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac tromethamine clearance or terminal half-life

COMBINATION TREATMENT:
Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly, and may require for optimal analgesic effect in the early postoperative period when pain is most severe. Ketorolac does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. When used in association with ketorolac ampoule, the daily dose of opioid is usually less than that normally required. However, opioid side effects should still be considered, especially in day-case surgery

CONTRAINDICATIONS:
- History of peptic ulcer or gastrointestinal bleeding
- Suspected or confirmed cerebrovascular bleeding
- Haemorrhagic diatheses, including coagulation disorders
- Patient 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 the complete or partial syndrome of nasal polyps, angioedema or bronchospasm
- Concurrent treatment with other NSAIDs, oxpentifylline, probenecid or lithium salts
- Hypovolaemia from any cause or dehydration
- Moderate or severe renal impairment (serum creatinine level >442 µmol/l)
- A history of asthma
- Known hyperkalemia
- Patients who have had operations with a high risk of haemorrhage or incomplete haemostasis
- Patients on anticoagulants including low dose heparin (2500 - 5000 units 12 hourly)
- During third trimester of pregnancy, labour, delivery or lactation
- Children under 18 years of age

WARNING AND PRECAUTIONS:

Risk of Cardiovascular (CV) Adverse, Events: Ischemic heart disease, cerebrovascular disease, congestive heart failure

Physicians should be aware that in some patients, pain relief might not occur until 30 minutes or more after I.V. or I.M. administration

Use in the elderly:
In common with other NSAIDs, patients over the age of 65 years may be at an increased risk of experiencing adverse events compared to younger patients. The elderly have an increased plasma half-life and reduced plasma clearance of ketorolac, therefore a total daily dose of greater than 60mg Ketorolac is not recommended

Gastro-intestinal effects: Ketorolac can cause gastro-intestinal irritation, ulcers or bleeding in patients with or without a history of previous symptoms. Elderly and debilitated patients are more prone to develop these reactions. The incidence increases with dose and duration of treatment. A study has shown increased rates of clinically serious GI bleeding in patients <65 years of age who received an average daily dose of >90mg ketorolac I.M. as compared to those patients receiving parenteral opioids

210mm

120mm

Respiratory effects: Bronchospasm may be precipitated in patients with a history of asthma

Renal effects: Drugs that inhibit prostaglandin biosynthesis (including non-steroidal anti-inflammatory drugs) 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 ketorolac and may occur after one dose.

Patients with impaired renal function: Since ketorolac and its metabolites are excreted primarily by the kidney, patients with moderate to severe impairment of renal function (serum creatinine >442 µmol/l) should not receive ketorolac injection. Patients with lesser renal impairment should receive a reduced dose of ketorolac (not exceeding 60mg/day I.M. or I.V.) and their renal status should be closely monitored

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. Meaningful elevations (greater than three times normal) of serum glutamate pyruvate transaminase (SGPT/ALT) or serum glutamate oxaloacetate transaminase (SGOT/AST) occurred in controlled clinical trials in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, ketorolac should be discontinued

Haematological effects: Patients with coagulation disorders should not receive Ketorolac. Patients on anti-coagulation therapy may be at increased risk of bleeding if given ketorolac concurrently. The concomitant use of ketorolac and prophylactic low-dose heparin (2500 - 5000 units twelve hourly) has not been studied extensively and may also be associated with an increased risk of bleeding. Patients already on anti-coagulants or who require low-dose heparin should not receive ketorolac. Patients who are receiving other drug therapy that interferes with haemostasis should be carefully observed if ketorolac is administered. In controlled clinical studies, the incidence of clinically significant post-operative bleeding was less than 1%.
Ketorolac inhibits platelet aggregation and prolongs bleeding time. In patients with normal bleeding function, bleeding times were raised, but not outside the normal range of two to eleven minutes. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24 to 48 hours after Ketorolac is discontinued

Post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of Ketorolac. Therefore, ketorolac should not be used in patients who have had operations with a high risk of haemorrhage or incomplete haemostasis. Caution should be used where strict haemostasis is critical, e.g. in cosmetic or day-case surgery. Haematomata and other signs of wound haemorrhage and epistaxis have been reported with the use of ketorolac. Physicians should be aware of the pharmacological similarity of ketorolac to other non-steroidal anti-inflammatory drugs that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly

Use in pregnancy & nursing mother: Safety in human pregnancy has not been established. Ketorolac is therefore contraindicated during pregnancy, labor or delivery. Ketorolac has been detected in human milk at low levels, it is also contraindicated in mothers who are breast-feeding. (There was no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of Ketorolac. Prolongation of the gestation period and/or delayed parturition was seen in the rat Ketorolac and its metabolites have been shown to pass into the fetus and milk of animals)

UNDESIRABLE EFFECTS

Gastro-intestinal tract: Nausea, dyspepsia, gastro-intestinal pain, gastro-intestinal bleeding, abdominal discomfort, haematemesis, gastritis, oesophagitis, diarrhoea, eructation, constipation, flatulence, fullness, melaena, peptic ulcer, non-peptic gastro-intestinal ulceration, rectal bleeding, ulcerative stomatitis & vomiting

Central nervous/musculoskeletal systems: Anxiety, drowsiness, dizziness, headache, sweating, dry mouth, nervousness, paraesthesia, functional disorders, abnormal thinking, depression, euphoria, convulsions, excessive thirst, inability to concentrate & insomnia

Renal: Nephrotoxicity including increased urinary frequency, oliguria, acute renal failure, hyponatraemia, hyperkalemia, haemolytic uraemic syndrome, flank pain (with or without haematuria), raised serum urea and creatinine, interstitial nephritis, urinary retention, nephrotic syndrome

Cardiovascular/haematological: Flushing, bradycardia, pallor, purpura, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, hypertension, palpitations, chest pain

Respiratory: Dyspnoea, asthma, pulmonary oedema

Dermatological: Pruritus, urticaria, skin photosensitivity, Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash

Hypersensitivity reactions: Anaphylaxis, bronchospasm, laryngeal oedema, hypotension, flushing and rash. Such reactions may occur in patients with or without known sensitivity to ketorolac or other non-steroidal anti-inflammatory drugs
These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma and nasal polyps). Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome

Bleeding: Post-operative wound haemorrhage, haematomata, epistaxis, increased bleeding time
Reproductive, female: Infertility
Other: Asthenia, oedema, weight gain, abnormalities of liver function tests, hepatitis, liver failure, jaundice, fever. Injection site pain has been reported in some patients

Overdose: Doses of 360mg given intramuscularly over an eight hour interval for five consecutive days have caused abdominal pain and peptic ulcers that have healed after discontinuation of dosing. Two patients recovered from unsuccessful suicide attempts. One patient experienced nausea after 210mg ketorolac, and the other hyperventilation after 300mg ketorolac

DRUG INTERACTIONS:
Ketorolac is highly bound to human plasma protein (mean 99.2%) and binding is concentration independent

Ketorolac should not be used with other NSAIDs or in patients receiving aspirin because of the potential for additive side-effects

Care should be taken when administering ketorolac with anti-coagulants since co-administration may cause an enhanced anti-coagulant effect

Ketorolac and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of beta-blockers and may increase the risk of renal impairment when administered concurrently with ACE inhibitors, particularly in volume depleted patients

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides

Ketorolac tromethamine reduces the diuretic response to furosemide by approximately 20% in normovolemic subjects, so particular care should be taken in patients with cardiac decompensation

Caution is advised when methotrexate is administered concurrently, since some prostaglandin synthesis inhibiting drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity

Probenecid should not be administered concurrently with ketorolac because of increases in ketorolac plasma level and half-life
As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity

Special Remarks:

Incompatibilities: Ketorolac injection 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 will occur

It is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmalyte solutions. Compatibility of ketorolac injection with other drugs is unknown

STABILITY:
See expiry on the pack

PRESENTATION:

TEKAC® 30mg/ml Injection in a pack of 5's

INSTRUCTIONS:
Discard any portion of the contents remaining after use
Keep out of reach of children
Avoid exposure to heat, light and freezing
Store between 15 to 30°C
Improper storage may deteriorate the medicine
Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s)

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

ٹیکیک® ۳۰ ملی گرام/ملی لیٹر انجکشن
(کیٹورولیک ٹرومیتھامین)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
استعمال کے بعد باقی بچ جانے والے محلول کو ضائع کردیں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہوجائیگی
انجکشن کے ایک ہونے، دُھندلا ہونے یا اس میں
کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں

R.N-02HA/11/19

210mm

120mm