Ketoroget™

[Ketorolac Tromethamine]

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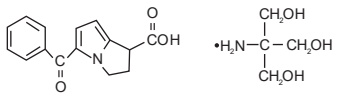
Solution for Injection 30mg/ml
(IV/ IM)

DESCRIPTION
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). Its molecular formula is $C_{15}H_{13}NO_3 \bullet C_4H_{11}NO_3$, and the structural formula is:



Ketorolac Tromethamine

QUALITATIVE AND QUANTITATIVE COMPOSITION
Ketoroget (Ketorolac Tromethamine) Solution for Injection is available for IV/IM administration as:

Ketoroget Solution for Injection 30mg/ml
Each 1ml of ampoule contains:
Ketorolac Tromethamine USP… 30mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ketorolac Tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity mediated by peripheral effects. The mechanism of action of Ketorolac Tromethamine, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics
Absorption
The IM form of Ketorolac Tromethamine is rapidly and completely absorbed (100% bioavailable). Steady state plasma levels are achieved after dosing every 6 hours for one day. A mean peak plasma concentration of 2.2µg/mL occurs an average of 50 minutes after a single 30mg dose. The IV administration resulted in peak plasma concentration of 2.4µg/mL occurring an average of 5.4 minutes after dosing.

Distribution
More than 99% of Ketorolac Tromethamine in plasma is protein bound. Even at high plasma concentrations (10µg/mL) only approximately 5% of albumin binding sites will be occupied. The mean apparent volume (V_d) of Ketorolac Tromethamine following complete distribution is approximately 13 liters.

Metabolism
Ketorolac Tromethamine is largely metabolized in the liver. The major metabolic path of Ketorolac Tromethamine in humans is glucuronic acid conjugation. P-hydroxylation is an additional minor pathway. The metabolism, and some unchanged Ketorolac Tromethamine is excreted predominantly by the urine averaged 92% in humans.

Excretion
The primary route of excretion of Ketorolac Tromethamine and its metabolites (conjugates and a para-hydroxy metabolite) is in the urine (mean 91.4%) and the remainder (mean 6.1%) is excreted in the feces. The terminal plasma half-life of Ketorolac Tromethamine is approximately in the range of 5-6 hours. No changes in clearance occur with chronic dosing.

Special Population
Elderly population
The half-life of the Ketorolac Tromethamine increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years). The total plasma clearance may be reduced compared to young healthy volunteer, on average of 0.019L/h/kg.

Renal impairment
The mean half-life of Ketorolac Tromethamine in renal-impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total Ketorolac Tromethamine clearance in the elderly and populations with renal impairment. In patients with renal disease, the AUC increases by approximately 100% compared with healthy volunteers. The volume of distribution increases by up to 100%.

Hepatic impairment
Patients with impaired hepatic function do not have any clinically important changes in Ketorolac Tromethamine pharmacokinetics, although there is a statistically significant prolongation of T_{max} and terminal phase half-life compared to young healthy volunteers.

THERAPEUTIC INDICATIONS
Ketoroget (Ketorolac Tromethamine) Injection is indicated for the short-term management of moderate to severe, acute pain including pain following major abdominal, orthopedic and gynecological operative procedures.

DOSAGE & ADMINISTRATION
General Dosing Consideration
Ketoroget (Ketorolac Tromethamine) Injection dosage should be adjusted according to the severity of the pain and the response of the patient. The lowest effective dose should be used for the shortest possible time in all patient populations. Treatment should only be initiated in hospital. The maximum duration of treatment is two days.

Adults
Dosage should be adjusted as per severity of the pain and the response of the patient.

IM/IV Administration
The recommended usual initial dose is 10mg to 30mg, according to the pain severity. Subsequent dosing may be 10mg to 30mg every 4-6 hours as needed to manage the pain.

The total daily dose must not exceed 90mg due to the risk of toxicity appears to increase with longer use at recommended doses.

Conversion from Parenteral to Oral Therapy
When Ketorolac Tromethamine tablets are used as follow-on therapy to parenteral, the total combined daily dose of Ketorolac Tromethamine (oral + parenteral) should not exceed 120mg in adult patients and 60mg in elderly patients on the day the change in formulation is made. The total duration of parenteral and oral administration should not exceed 5 days.

Missed Dose
The missed dose should be taken as soon as remembered, and then the regular dosing schedule should be continued. Two dose of Ketoroget Injection must not be taken at same time.

Special Population
Elderly population
An initial dose of 10mg to 15mg, followed by 10mg to 15mg at 4 to 6 hourly intervals, up to a maximuam daily dose of 60mg.

Patient with renal impairment
Patients with mildly impaired renal function (serum creatinine values: males between 130 and 180 micromol/L; females between 120 and 180 micromol/L) the lower end of the dosage range should be used. The total daily dose should not exceed 60mg.

ADVERSE REACTIONS
The following undesirable effects may occur in patients receiving Ketorolac Tromethamine.
Gastro-intestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, nausea, dyspepsia, abdominal pain/discomfort, hematemesis, stomatitis, dry mouth, esophagitis, diarrhea, eructation, constipation, flatulence, fullness, melena, gastro-intestinal ulceration, rectal bleeding, ulcerative stomatitis, vomiting, pancreatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.
Blood and Lymphatic system disorders: Thrombocytopenia, purpura, neutropenia, agranulocytosis, aplastic anemia and hemolytic anemia.
Immune System Disorders: Anaphylaxis, anaphylactoid reactions, anaphylactoid reactions like anaphylaxis, may have a fatal outcome, hypersensitivity reactions such as bronchospasm flushing, rash, hypotension, laryngeal edema. These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma and nasal polyps).
Infection: Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.
Metabolic and nutrition disorders: Anorexia, hyponatremia, hyperkalemia.
Psychiatric disorders: Abnormal thinking, depression, euphoria, insomnia, anxiety, nervousness, psychotic reactions, abnormal dreams, hallucinations, inability to concentrate, drowsiness, confusion and stimulation.
Nervous system disorders: Dizziness, headache, paraesthesia, convulsions, abnormal taste and hyperkinesia.
Eye disorders: Optic neuritis, abnormal vision and visual disturbances.
Ear disorders: Hearing loss, tinnitus and vertigo.
Renal and urinary disorders: Increased urinary frequency, oliguria, acute renal failure, hemolytic uremic syndrome, flank pain (with or without hematuria and/or azotemia), interstitial nephritis, urinary retention, nephrotic syndrome. As with other drugs that inhibit renal prostaglandin synthesis signs of renal impairment, such as, but not limited to elevations of creatinine and potassium can occur after one dose of Ketorolac Tromethamine.
Cardiac disorders: Bradycardia, palpitations and cardiac failure.
Vascular disorders: Flushing, pallor, hypertension, edema, hypotension, postoperative wound hemorrhage and hematoma.
Reproductive system and breast disorders: Female infertility.
Hepatobiliary disorders: Hepatitis, cholestatic jaundice and liver failure.
Skin and subcutaneous tissue disorders: Pruritus, urticaria, purpura, angioedema, exfoliative dermatitis, maculopapular rash, sweating, bullous reactions including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (very rare). Additionally, erythema multiforme and skin photosensitivity has been observed.
Musculoskeletal and Connective Tissue Disorders: Myalgia and functional disorder.
General Disorders and Administration Site Condition: Excessive thirst, asthenia, weight gain, fever, injection site reactions and pain, chest pain, malaise and fatigue.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Ketorolac Tromethamine is contraindicated:
- In patients with a known hypersensitivity of this drug or to any of the excipient of the product.
- In patients with severe heart failure, or undergoing treatment of pre-operative setting of coronary artery bypass graft (CABG).
- In patients with dehydration or hypovolemia from any other cause.
- In patients with severe hepatic impairment.
- In patients with moderate or severe renal impairment (serum creatinine > 180 micromol/L), or in patients at risk of renal failure due to volume depletion or dehydration.
- In patients with active, or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- In patients with Active, or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients with a history of hemorrhagic diatheses, including coagulation disorders.
- In patients with have had surgery with a high risk of hemorrhage or incomplete hemostasis; and those at high risk of bleeding.
- In patients with suspected or confirmed cerebrovascular (intracranial) bleeding.
- In patients with anticoagulation therapy.
- In patients receiving aspirin, other NSAIDs, oxpentifylline, probenecid or lithium.
- In patients with hypersensitivity to or other NSAIDs and those patients in whom

aspirin or other prostaglandin synthetase inhibitors induce allergic reactions. Severe anaphylactic-like reactions have been observed in such patients. If such symptoms occur during therapy, treatment should be discontinued.
- In patients with the complete or partial syndrome of nasal polyps, angioedema or bronchospasm.
- In patients with a history of asthma.
- In patients with a prior history of Stevens-Johnson syndrome or vesicular bullous rash.
- In prophylactic administration before surgery, due to inhibition of platelet aggregation; and intraoperatively because of the increased risk of bleeding.
- For neuraxial (epidural or intrathecal) administration due to its alcohol content.
- During pregnancy, labor or delivery and lactation.
- In children and adolescents under 16 years of age.

WARNINGS AND PRECAUTIONS

Oral Ketorolac Tromethamine is indicated only as continuation treatment following IV or IM dosing of Ketorolac Tromethamine, if necessary. The total combined duration of use of oral Ketorolac Tromethamine and Ketorolac Tromethamine injection should not exceed 5 days.
Ketorolac Tromethamine is not indicated for use in pediatric patients and it is NOT indicated for minor or chronic painful conditions. Increasing the dose of Ketorolac Tromethamine beyond the label recommendations will not provide better efficacy but will increase the risk of developing serious adverse events.

Gastrointestinal Risk
Ketorolac Tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms, elderly patients are at greater risk for serious gastrointestinal events.

Cardiovascular Risk
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

General: The total combined duration of use of oral Ketorolac Tromethamine and IV or IM dosing of Ketorolac Tromethamine is not to exceed 5 days in adults. Ketorolac Tromethamine cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
Gastro-intestinal bleeding, ulceration and perforation: Ketorolac Tromethamine may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially when used for prolonged period. GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including Ketorolac Tromethamine therapy, at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Respiratory effects: Caution is required if administered to patients suffering from, or with a previous history of, bronchial spasm since NSAIDS have been reported to precipitate bronchospasm in such patients.
Renal effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Ketorolac Tromethamine should be used with caution in patients with impaired renal function and such patients should be followed closely. There have been reports of acute renal failure, interstitial nephritis and nephrotic syndrome with the use of Ketorolac Tromethamine.
SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.
Skin reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
Precautions related to female fertility: The use of Ketorolac Tromethamine, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive.
Sodium/fluid retention in cardiovascular conditions and peripheral edema: Caution is required in patients with a history of hypertension and /or heart failure as fluid retention and edema have been reported in association with NSAID therapy. Fluid retention, hypertension and peripheral edema has been observed in some patients taking NSAIDs including Ketorolac Tromethamine and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.
Anaphylactic (anaphylactoid) reactions: Anaphylactic (anaphylactoid) reactions (including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal edema and angioedema) may occur in patients with or without a history of hypersensitivity to aspirin other NSAIDs or Ketorolac Tromethamine.
Hematological effects: Patients with coagulation disorders should not receive Ketorolac Tromethamine. Patients on anti-coagulation therapy may be at increased risk of bleeding if given Ketorolac Tromethamine concurrently.

Effects on ability to drive and use machines
Some patients may experience dizziness, drowsiness, visual disturbances, headaches, vertigo, insomnia or depression with the use of Ketorolac Tromethamine. If patients experience these, or other similar undesirable effects, they should not drive or operate machinery.

DRUG INTERACTIONS
The following medicinal products are NOT to be co-administered with Ketorolac Tromethamine Injection
NSAIDs/Aspirin: Ketorolac Tromethamine should not be used with other NSAIDs including cyclooxygenase-2 selective inhibitors or in patients receiving aspirin because of the increased risk of inducing serious NSAID-related adverse effects.
Thromboxane: Ketorolac Tromethamine inhibits platelet aggregation, reduces thromboxane concentrations and prolongs bleeding time. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24-48 hours after Ketorolac Tromethamine is discontinued.
Anticoagulants: Ketorolac Tromethamine injection is contraindicated in combination with anti-coagulants, such as warfarin since co-administration may cause an enhanced anti-coagulant effect.
Lithium: In patients receiving lithium, there is a possible inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration with some prostaglandin synthesis-inhibiting drugs.
Mifepristone: NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.
Oxpentifylline: When Ketorolac Tromethamine is administered concurrently with oxpentifylline, there is an increased tendency to bleeding.

The following medicinal products in combination with Ketorolac Tromethamine, are to be co-administered with caution.
Diuretics: Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAID.
Diuretics and Anti-hypertensive: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE inhibitors and/or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately titrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.
Methotrexate: 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.
Cyclosporine: As with all NSAIDs caution is advised when cyclosporine is co-administered because of the increased risk of nephrotoxic.
Corticosteroids: As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastro-intestinal ulceration or bleeding
Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): There is an increased risk of gastrointestinal bleeding when anti-platelet agents and SSRIs are combined with NSAIDs.
Tacrolimus: There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine: NSAIDs given with zidovudine increase the risk of hematological toxicity. There is evidence of an increased risk of hematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Digoxin: The effects of Ketorolac Tromethamine has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.
Antiepileptic Drugs: Sporadic cases of seizures have been reported during concomitant use of Ketorolac Tromethamine and antiepileptic drugs (phenytoin, carbamazepine).
Psychoactive Drugs: Hallucinations have been reported when Ketorolac Tromethamine was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).
Ketorolac Tromethamine has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.

OVERDOSAGE
Symptoms
Overdoses of Ketorolac Tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment
Patients should be managed by symptomatic and supportive care following NSAID overdose. There are no specific antidotes. Dialysis does not significantly clear Ketorolac Tromethamine from the blood stream.

STORAGE
Do not store above 30°C.
Protect from light and heat. Do not refrigerate or freeze.

Ketoroget (Ketorolac Tromethamine) Solution for Injection 30mg/ml is for single use only. Do not use if particulate matter is present in the solution. Discard any portion of the content remaining after use.

Ketoroget (Ketorolac Tromethamine) Solution for Injection 30mg/ml 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. It is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmacyte solutions. Compatibility of Ketorolac Tromethamine Injection with other drugs is unknown.

The expiration date refers to the product correctly stored at the recommended conditions.

HOW SUPPLIED
Ketoroget (Ketorolac Tromethamine) Solution for Injection 30mg/ml (IM/IV) is available in pack of 5 x 1ml ampoules.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
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