

# Actrolac Inj.

(Ketorolac Tromethamine USP)

ایکٹرو لک انجکشن  
(کیٹورولک ٹرومیتھامین یو ایس پی)

## WARNING

Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term management of moderately severe acute pain that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom Ketorolac is indicated, especially when the drug is used inappropriately. Increasing the dose of Ketorolac beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

**Gastrointestinal Effects:** Ketorolac can cause peptic ulcers, gastrointestinal bleeding and/or perforation. Therefore, it is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

**Renal Effects:** Ketorolac is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.

**Risk of Bleeding:** Ketorolac inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding. Ketorolac is CONTRAINDICATED as prophylactic analgesic before any major surgery and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.

**Hypersensitivity:** Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of Ketorolac Injection. Ketorolac is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to Ketorolac or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

**Intrathecal or Epidural Administration:** Ketorolac is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

**Labor, Delivery and Nursing:** The use of Ketorolac in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and the uterus. The use of Ketorolac is CONTRAINDICATED in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.

**Concomitant Use With NSAIDs:** Ketorolac is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

**Dosage and Administration:** The combined duration of use of Ketorolac Injection and Ketorolac tablets is not to exceed five (5) days because of the increased risk of serious adverse events. The maximum total daily dose of Ketorolac Injection is 120 mg.

**Special Populations:** Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine. Doses of Ketorolac Injection are not to exceed 60 mg (total dose per day) in these patients.

## COMPOSITION

Each **Actrolac** ampoule contains 30 mg of Ketorolac in 1 ml of solution.

## MECHANISM OF ACTION

Ketorolac inhibits key pathways in prostaglandin synthesis which is crucial to its mechanism of action. Although Ketorolac is non-selective and inhibits both COX-1 and COX-2 enzymes, its clinical efficacy is derived from its COX-2 inhibition. The COX-2 enzyme is inducible and is responsible for converting arachidonic acid to prostaglandins that mediate inflammation and pain. By blocking this pathway, Ketorolac achieves analgesia and reduces inflammation.

## PHARMACOKINETIC

**IM:** Following intramuscular administration, Ketorolac was rapidly and completely absorbed, a mean peak plasma concentration occurring an average of 50 minutes after a single 30mg dose.

**IV:** Intravenous administration of a single 10mg dose of Ketorolac resulted in a mean peak plasma concentration occurring an average of 5.4 minutes after dosing, with a terminal plasma elimination half-life of 5.1 hours. Steady-state plasma levels are achieved after dosing every six hours for one day. No changes in clearance occurred with chronic dosing.

**Metabolism:** Ketorolac is heavily metabolized via hydroxylation or conjugation in the liver; however, it appears that the key metabolic pathway is glucuronic acid conjugation. More than 99% of the Ketorolac in plasma is protein-bound over a wide concentration range.

**Route of elimination:** The primary route of excretion of Ketorolac and its metabolites is renal. Approximately 92% of the dose can be recovered in the urine with 60% of this proportion recovered unchanged, and 40% recovered as metabolites. In addition, 6% of a single dose is eliminated in the feces.

**Half-life:** Ketorolac is administered as a racemic mixture, therefore the half-life of each enantiomer must be considered. The half-life of the S-enantiomer is ~2.5 hours, while the half-life of the R-enantiomer is ~5 hours. Based on this data, the S enantiomer is cleared about twice as fast as the R enantiomer.

## INDICATIONS

It is indicated for short term management of acute pain that requires the calibre of pain management offered by opioids. Clinicians may choose to initiate Ketorolac to manage post-operative pain, spinal and soft tissue pain, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, menstrual disorders and headaches among other ailments. Regardless of the etiology of pain, patients should use the lowest possible dose, and avoid using Ketorolac for an extended period of time (ideally ≤ 5 days). A benefit of choosing Ketorolac over other analgesics with similar potency is that there does not appear to be a risk of dependence or tolerance with Ketorolac use.

## DOSAGE AND ADMINISTRATION

**Actrolac** 30 mg/ml solution for injection is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over no less than 15 seconds. **Actrolac** 30 mg/ml solution for injection should not be used for epidural or spinal administration.

The time to onset of analgesic effect following both IV and IM administration is approximately 30 minutes, with maximum analgesia occurring within one to two hours. The median duration of analgesia is generally four to six hours.

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

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.

## ADVERSE EFFECTS

- Adverse reaction rates increase with higher doses of Ketorolac. Practitioners should be alert for the severe complications of treatment with Ketorolac, such as bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure.
- The most frequently reported adverse experiences in approximately 1% to 10% of patients taking Ketorolac or other NSAIDs in clinical trials are nausea, headache, abdominal pain, vomiting, flatulence, gross GI bleeding/perforation, stomatitis, constipation/ diarrhea, heartburn, dyspepsia and GI ulcers (gastrointestinal).
- Other adverse experiences are abnormal renal function, drowsiness, injection site pain, rash, anemia, edema, hypertension, pruritus, tinnitus, dizziness, elevated liver enzymes, increased bleeding and sweating.

## DRUG INTERACTIONS

The following medicinal products are NOT to be co-administered with Ketorolac 30 mg/ml solution for injection:

- ASA or other NSAIDs including cyclooxygenase-2 selective inhibitors.
- Anti-coagulants, such as warfarin, heparin and dextrans.
- Cases of increased lithium plasma concentrations during Ketorolac therapy have been reported.
- Probenecid should not be administered concurrently with Ketorolac because of increases in Ketorolac plasma concentrations and half-life.
- NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

The following medicinal products in combination with Ketorolac 30 mg/ml solution for injection are to be co-administered with caution:

- Caution should be taken when co-administering with corticosteroids because of the increased risk of gastro-intestinal ulceration or bleeding.
- There is an increased risk of gastrointestinal bleeding when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.
- When Ketorolac is administered concurrently with oxpentifylline, there is an increased tendency to bleeding.
- Some prostaglandin synthesis-inhibiting drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.
- Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter Ketorolac protein binding.
- Ketorolac Solution for injection reduced the diuretic response to furosemide in normovolemic healthy subjects by approximately 20% so particular care should be taken in patients with cardiac decompensation.
- Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.
- As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.
- There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- ACE inhibitors and/or angiotensin II receptor antagonists combination should be administered with caution, especially in the elderly.

- NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.
- Ketorolac has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.
- 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.
- NSAIDs given with zidovudine increase the risk of haematological toxicity.

## WARNINGS

- To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.
- Use of Ketorolac in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored.
- Peri-operative use of Ketorolac should be avoided and postoperative use be undertaken with caution when hemostasis is critical.
- Ketorolac should be used with caution in patients with impaired renal function. There have been reports of acute renal failure, interstitial nephritis, and nephrotic syndrome.
- Anaphylactoid reactions may occur in patients without known prior exposure to Ketorolac. Ketorolac should not be given to patients with the aspirin.
- To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible.
- Avoid the use of Ketorolac Injection in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Ketorolac Injection is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.
- NSAIDs, including Ketorolac can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Ketorolac, should be used with caution in patients with hypertension.
- Fluid retention and edema have been observed in some patients treated with NSAIDs. Avoid the use of Ketorolac Injection in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Ketorolac Injection is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.
- NSAIDs, including Ketorolac can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning.
- In late pregnancy, as with other NSAIDs, Ketorolac should be avoided because it may cause premature closure of the ductus arteriosus.

## PRECAUTIONS

- Ketorolac cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency.
- Ketorolac should be used with caution in patients with impaired hepatic function or a history of liver disease. Border-line elevations of one or more liver tests may occur in up to 15% of patients.
- Anemia is sometimes seen in patients receiving NSAIDs, including Ketorolac. Patients receiving Ketorolac who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.
- Ketorolac should not be administered to patients with aspirin sensitivity and should be used with caution in patients with pre-existing asthma.
- The use of Ketorolac as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive.
- Exercise caution when Ketorolac is administered to a nursing woman.
- Ketorolac is not indicated for use in pediatric patients. The safety and effectiveness of Ketorolac in pediatric patients below the age of 17 have not been established.
- Extreme caution and reduced dosages and careful clinical monitoring must be used when treating the elderly with Ketorolac.

## PREGNANCY AND LACTATION

In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) Ketorolac is contra-indicated during pregnancy, labour or delivery.

The safety of Ketorolac 30 mg/ml solution for injection during human pregnancy has not been established.

## Labor and Delivery:

Ketorolac is contraindicated in Labour and delivery because, through its prostaglandin synthesis inhibitory effect it may adversely affect foetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage. There may be increased bleeding tendency in both mother and child.

## Nursing Mothers:

Ketorolac has been detected in human milk at low concentrations; therefore, Ketorolac is contra-indicated in mothers who are breast-feeding.

## Effects on ability to drive and use machines:

Some patients may experience dizziness, drowsiness, fatigue, visual disturbances, headaches, vertigo, insomnia or depression with the use of Ketorolac 30 mg/ml solution for injection. If patients experience these, or other similar undesirable effects, patients should not drive or operate machinery.

## CONTRAINDICATIONS

Ketorolac is contraindicated in:

- Patients with previously demonstrated hypersensitivity to Ketorolac, any of its excipients, 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). Such reactions have included asthma, rhinitis, angioedema, or urticaria.
- Patient with a history of asthma
- Children under 16 years of age.
- Patients with active or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Patients with severe heart failure, hepatic failure and renal failure.
- Patients with moderate or severe renal impairment or in patients at risk for renal failure due to volume depletion or dehydration.
- Pregnancy, labour, delivery or lactation.
- As prophylactic analgesia before surgery due to inhibition of platelet aggregation and is contra-indicated intra-operatively because of the increased risk of bleeding.
- Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients who have had operations with a high risk of haemorrhage or incomplete haemostasis and those at high risk of bleeding such as those with haemorrhagic diatheses, including coagulation disorders.
- Patients on anticoagulants, including warfarin and low dose heparin (2500 - 5000 units 12 hourly).
- Patients currently receiving ASA or other NSAIDs (including cyclooxygenase-2 selective inhibitors).
- Ketorolac Solution for injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.
- The combination of Ketorolac with oxpentifylline is contraindicated. Concurrent treatment with Ketorolac and probenecid or lithium salts is contraindicated.
- Patients with the complete or partial syndrome of nasal polyps, angioedema or bronchospasm.

## OVERDOSE

- Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
- Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Dialysis does not significantly clear Ketorolac from the blood stream.

## PRESENTATION

**Actrolac** 30mg IM/IV Inj.: 5x1ml Ampoule

## DOSAGE:

As directed by the physician.

## INSTRUCTIONS:

Store in a cool & dry place below 30°C.

Keep out of reach of children.

Protect from light, heat & moisture.

Do not use if ampoule is leaking, solution is turbid or contains any foreign matter.

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

Manufactured by:  
**AsianContinental (Pvt.) Ltd.**  
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Karachi-Pakistan.



An ISO Certified Company

Manufactured by:  
**Wimits Pharmaceuticals (Pvt.) Ltd.**  
129-Sunder Industrial Estate, Lahore.  
M. L. No.: 000789  
Reg. No.: 114313

خبراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔  
ہدایت: دو ایکوینڈنٹی اور خشک جگہ پر ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔  
تمام دواؤں میں بچوں کی ہتھی سے دور رکھیں۔  
دوا کو روشنی، گرمی اور دھوپ سے بچائیں۔  
انجکشن کے ایک ہونے، دھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔  
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔