KEI3 MYS-002
R.O.C. Reg. No.:042412

KETO INJECTION 30MG/ML

Ingredient(s):
Each mL contains:
Ketorolac Tromethamine 30mg

Pharmacology (Summary of Pharmacodynamics and Pharmacokinetics):
1. Ketorolac is a nonsteroidal agent with potent analgesic, anti-inflammatory and antipyretic activity. It inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase, an enzyme that catalyzes the formation of prostaglandin precursors (endoperoxides) from arachidonic acid. Ketorolac does not have any known effects on opiate receptors.
2. Ketorolac is completely absorbed following intramuscular administration with mean peak plasma concentrations of 2.2-3.0 μg/mL occurring an average of 50 minutes after a single 30 mg dose. The terminal plasma half-life is 3.5-9.2 hours in young adults and 4.7-8.6 hours in elderly subjects (mean age 72).
3. Following oral, IM, or IV administration, Ketorolac and its metabolites are excreted mainly in urine; only small amounts of the drug and its metabolites are excreted in faeces, probably via biliary elimination. The primary route of excretion of Ketorolac and its metabolites (conjugates and the p-hydroxy metabolite) is in the urine (91.4%) with the remainder (6.1%) being excreted in the faeces. Ketorolac is almost totally bound to plasma proteins (more than 99%) and its apparent volume of distribution is 0.25 L/kg or less.

Indication(s):
For short-term management of moderate to severe acute post-operative pain following surgical procedures associated with low risk of hemorrhage.

Dosage and Administration:
KETO INJECTION are for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over no less than 15 seconds. KETO INJECTION should not be used for epidural or spinal administration. The time to onset of analgesic effect following both IV and IM 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 KETO INJECTION intramuscularly or intravenously should not exceed 2 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 starting dose should be 10 mg with subsequent doses of 10-30 mg four to six hourly as required. The lowest effective dose should be used. The total daily dose of 90 mg for the non-elderly and 60 mg for the elderly should not be exceeded. Maximum duration of the parenteral treatment is 2 days for all age groups. In patients who have received parenteral Ketolac and are converted to oral tablets, the total combined daily dose of all forms of Ketorolac should not exceed 90 mg for non-elderly and 60 mg for elderly. Maximum duration of treatment for the oral formulation is 7 days.
Route of Administration: By intramuscular or bolus intravenous injection.

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.
Children: Safety and efficacy in children have not been established. Therefore, KETO INJECTION is contraindicated for use in children under 16 years of age.
Renal impairment: Since Ketorolac trometamol and its metabolites are excreted primarily by the kidney, KETO INJECTION is contraindicated in moderate to severe renal impairment (serum creatinine>160 μmol/L): patients with lesser renal impairment should receive a reduced dose (not exceeding 60 mg per day IV or IM), and their renal status should be closely monitored. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Contraindication(s):
1. A history of peptic ulceration or gastrointestinal bleeding.
2. A history of haemorrhagic diathesis.
3. A history of confirmed or suspected cerebrovascular bleeding.
4. Operations associated with a high risk of haemorrhage.
5. A history of asthma.
6. Moderate or severe renal impairment (serum creatinine>160 μmol/L).
7. Hypovolaemia or dehydration from any cause.
8. Hypersensitivity to NSAIDs or aspirin.
9. During pregnancy, labour, delivery or lactation.
10. Concomitant administration with other NSAIDs, anticoagulant including low dose heparin.

Precaution(s) / Warning(s):
1. **Cardiovascular Thrombotic Events.** Observational studies indicated that nonselective NSAIDs may be associated with an increased risk of serious cardiovascular events, principally myocardial infarction, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk of an adverse cardiovascular event in patient taking NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration. There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.
2. **Hypertension.** NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired antihypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.
3. **Heart Failure.** Fluid retention and oedema have been observed in some patients taking NSAIDs, hence caution is advised in patients with fluid retention or heart failure.
4. **Gastrointestinal Events.** All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Caution is advised in patients with risk factors for gastrointestinal events e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patient about signs and symptoms of serious gastrointestinal toxicity. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.
5. **Severe Skin Reactions.** NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.
6. **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 (2,500-5,000 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.
7. Ketorolac is a potent inhibitor of prostaglandin synthesis. Reduction in renal blood flow has been observed as prostaglandins have supportive role in the maintenance of renal perfusion. Patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risk and benefits should be assessed prior to giving Ketorolac to these patients.
8. Ketorolac may cause elevations of liver enzymes. In patients with pre-existing liver dysfunction, it may lead to the development of a more severe hepatic reaction.
9. Anaphylactoid reactions may occur in individuals with a history of angioedema, bronchospasm activity (eg. Asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have the fatal outcome.
10. **Use in the elderly:** Patients over the age of 65 years may be at greater risk of experiencing adverse events than younger patients. This age related risk is common to all NSAIDs. Compared to young adult, the elderly have an increased plasma half-life and reduced plasma clearance of Ketorolac. With KETO INJECTION, a total daily dose greater than 60 mg is not recommended.
11. **Effects on fertility:** The use of KETO INJECTION, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation for fertility, withdrawal of KETO INJECTION should be considered.
12. **Respiratory effects:** Bronchospasm may be precipitated in patients with a history of asthma.
13. **Fluid retention and oedema:** fluid retention and oedema have been reported with the use of KETO INJECTION and it should therefore be used with caution in patient with cardiac decompensation, hypertension or similar conditions.

Interaction with Other Medicaments:
1. KETO INJECTION should not be used with other NSAIDs or in patients receiving aspirin because of the potential for additive side-effects.
2. Ketorolac is highly bound to human plasma protein (mean 99.2%) and binding is concentration-independent.
3. Ketorolac did not alter digoxin protein binding. *In vitro* studies indicated that at therapeutic concentrations of salicylate (300 μg/mL) and above, the binding of Ketorolac was reduced from approximately 99.2% to 97.5%. Therapeutic concentrations of digoxin, warfarin, paracetamol, phenytoin and tolbutamide did not alter Ketorolac protein binding. Because Ketorolac is a highly potent drug and present in low concentrations in plasma, it would not be expected to displace other protein-bound drugs significantly.
4. Care should be taken when administering KETO INJECTION with anti-coagulants since co-administration may cause an enhanced anti-coagulant effect.
5. There is no evidence in animal or human studies that Ketorolac trometamol induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Hence KETO INJECTION would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.
6. In normovolaemic healthy subjects, Ketorolac reduces the diuretic response to frusemide by approximately 20%, so particular care should be taken in patients with cardiac decompensation.
7. KETO INJECTION and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of beta-blockers and may increase the risk of renal impairment when administered concurrently with ACE inhibitors, particularly in volume depleted patients.
8. NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.
9. 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.
10. Probenecid should not be administered concurrently with Ketorolac because of increases in Ketorolac plasma level and half-life.
11. As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity.
12. NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.
13. As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastro-intestinal bleeding.
14. Patients taking quinolones may have an increased risk of developing convulsions.
15. Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.
16. Because of an increased tendency to bleeding when oxpentifylline is administered concurrently, this combination should be avoided.
17. In patients receiving lithium, there is a possible inhibition of renal lithium clearance, increased plasma lithium concentration, and potential lithium toxicity.

WARNINGS
RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (eg. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (eg. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Pregnancy and Lactation:
There was no evidence of teratogenicity in rats or rabbits studies at maternally-toxic doses of Ketorolac. Prolongation of the gestation period and/or delayed parturition were seen in the rat. Ketorolac and its metabolites have been shown to pass into the foetus and milk of animals. Ketorolac has been detected in human milk at low levels. Safety in human pregnancy has not been established. Congenital abnormalities have been reported in association with NSAID administration in man, however these are low in frequency and do not follow any discernible pattern. Ketorolac is therefore contra-indicated during pregnancy, labour or delivery, or in mothers who are breast-feeding.

Side Effect(s) / Adverse Reaction(s):
The following side-effects have been reported with Ketorolac.
Gastro-intestinal: 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, haemorrhage, perforation, pancreatitis.
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, malaise, fatigue, stimulation, vertigo, abnormal taste and vision, optic neuritis, myalgia, abnormal dreams, hallucinations, hyperkinesia, hearing loss, tinnitus, aseptic meningitis, psychotic reactions.
Renal: Nephrotoxicity including increased urinary frequency, oliguria, acute renal failure, hyponatraemia, hyperkalaemia, 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.
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particulary at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Reproductive, female: Infertility.
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 KETO INJECTION 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.
Other: Asthenia, oedema, weight gain, abnormalities of liver function tests, hepatitis, liver failure, jaundice, fever. Injection site pain has been reported in some patients.

Symptoms and Treatment for Overdosage and Antidote(s):
Daily doses of 360 mg given over an 8-hour interval for each of five consecutive days (3 times the highest recommended dose) caused pain and peptic ulcers which resolved after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage. Single doses 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. Dialysis does not appreciably clear Ketorolac from the blood stream.

Shelf-life :
2 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 30°C. Protect from light and moisture.

Product description and Packing(s):
A clear and slight yellow liquid in ampoules.
1mLx 10 ampoules/box

Manufacturer:
YUNG SHIN PHARMACEUTICAL IND. CO., LTD.
Taichung Youth Factory
NO. 27, KUNG CHIU RD.,
TACHIA, TAICHUNG, TAIWAN, R.O.C.
Importer & Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
Lot 3, 5, 7, 12 & 14, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor, Malaysia.
Ordering Line: 1 800 88 3027
Product Info Line: 1 800 88 3679