TROMIT

(Ketorolac Tromethamine) USP

INJECTION

PHARMACEUTICAL FORM
Solution for injection

COMPOSITION
Each 1ml ampoule contains: Ketorolac Tromethamine (USP).....30mg

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS: TROMIT ampoules are indicated for the short-term management of moderate to severe acute postoperative pain.

DOSAGE AND METHOD OF ADMINISTRATION
TROMIT ampoules are for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over no less than 15 seconds. TROMIT ampoules 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, 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 TROMIT 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: AMPOULES: The recommended initial dose of TROMIT is 10 mg. followed by 10-30mg every 4 to 6 hours as required. In the initial postoperative period, TROMIT may be given as often as every 2 hours if needed. The lowest effective dose should be given. A total daily dose of 90mg for non-elderly and 60mg for the elderly, renally-impaired patients and patients less than 50 kg should not be exceeded. The maximum duration of treatment should not exceed 2 days.
For patients receiving TROMIT ampoules, and who are converted to tablets, the total combined daily dose should not exceed 90mg (60mg for the elderly, renally-impaired patients and patients less than 50 kg) and 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 PATIENTS: AMPOULES: For patients over 65 years, the lower and of the dosage range is recommended; a total daily dose of 60mg should not be exceeded (see SPECIAL WARNING AND PRECAUTIONS).

CHILDREN: Children ≥ 2 years of age
Single dose treatment I.M. dosing: One dose of 1.0 mg/kg. I.V. dosing: One dose of 0.5-1.0 mg/kg.

MULTIPLE DOSE TREATMENT: 1.0 mg/kg I.M. or 0.5-1.0 mg/kg I.V., followed by 0.5 mg/kg I.V. 6 hourly.

RENAL IMPAIRMENT: Since ketorolac tromethamine and its metabolites are excreted primarily by the kidney, TROMIT is contraindicated in moderate to severe renal impairment (Serum creatinine >160 micromol/l); patients with lesser renal impairment should receive a reduced dose (not exceeding 60 mg/day I.V. or I.M.) and their renal status should be closely monitored.

COMBINATION TREATMENT: (**See also INCOMPATIBILITIES**) Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly, and may be required for optimal analgesic effect in the early postoperative period when pain is most severe. Ketorolac tromethamine does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. When used in association with TROMIT ampoules, 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
TROMIT is contraindicated in patients with active peptic ulcer disease (as are other NSAIDs in patients with recent gastrointestinal bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. TROMIT is contraindicated in patients with moderate or severe renal impairment (serum creatinine >442 micro mol/l) or in patients at risk for renal failure due to volume depletion, or dehydration. TROMIT is contraindicated in labour and delivery.
TROMIT is contraindicated in patients with previously demonstrated hypersensitivity to TROMIT 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 (**see SPECIAL WARNING AND PRECAUTIONS**).
TROMIT is contraindicated as prophylactic analgesic before surgery due to inhibition of platelet aggregation and is contraindicated intra-operatively because of the increased risk of bleeding.
TROMIT 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 hemorrhage or incomplete hemostasis and those at high risk of bleeding (**see SPECIAL WARNINGS AND PRECAUTIONS**).
TROMIT is contraindicated in patients currently receiving ASA or other NSAIDs (**See INTERACTIONS**).
TROMIT Solution for injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Gastrointestinal Ulceration, Bleeding and Perforation
Gastrointestinal mucosal injury may occur. Serious gastrointestinal toxicity, such as, but not limited to gastrointestinal irritation bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs including TROMIT. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Post-marketing experience with parenterally administered TROMIT and with other NSAIDs suggests that there may be a greater risk of gastrointestinal ulceration, bleeding and perforation in the elderly and in debilitated patients who seem to tolerate ulceration or bleeding less well than other individuals. Most spontaneous reports of fatal GI events are in this population.
As with other NSAIDs, the incidence and severity of gastrointestinal complications may Increase with Increasing dose and duration of treatment with TROMIT. The risk of clinically serious gastrointestinal bleeding is dose-dependent. This is particularly true in elderly patients who receive an average daily dose greater than 60 mg/day of TROMIT. A history of peptic ulcer disease Increases the possibility of developing serious gastrointestinal complications during TROMIT therapy.

RENAL EFFECTS: As with other NSAIDs, TROMIT should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Caution should be observed as renal toxicity has been seen with TROMIT and other NSAIDs, in patients with conditions leading to a reduction in blood volume and/or renal blood flow where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of TROMIT or other NSAIDs may cause a dose-dependent reduction in renal prostaglandins formation and may precipitate overt renal decompensation or failure. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, those taking diuretics and the elderly (**see CONTRAINDICATIONS**). Discontinuation of TROMIT or other non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

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 TROMIT. 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 (**see CONTRAINDICATIONS**). Therefore, TROMIT should be used with caution in patients with a history of asthma and in patients with the complete or partial syndrome of nasal polyps, angioedema and bronchospasm.

HEMATOLOGICAL EFFECTS: TROMIT 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 TROMIT is discontinued. The use of TROMIT in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Although studies do not indicate a significant interaction between TROMIT and warfarin or heparin the concurrent use of TROMIT and therapy that affects hemostasis, including therapeutic doses of anticoagulation therapy (warfarin), prophylactic low-dose heparin (2500-5000 units 12-hourly) and dextrans may be associated with increased risk of bleeding. The administration of TROMIT to such patients should be done extremely cautiously, and these patients should be closely monitored (**see INTERACTIONS**).

In post-marketing experience, postoperative hematomas, and other signs of wound bleeding have been reported in association with the preoperative use of TROMIT Solution for injection. Physicians should be aware of the potential risk of bleeding when hemostasis is critical in cases such as, but not limited to, resection of the prostate, tonsillectomy or cosmetic surgery (**see CONTRAINDICATIONS**).
PRECAUTIONS IN ELDERLY PATIENTS: Elderly patients may be at a greater risk of experiencing undesirable effects than younger patients. This age-related risk is common to all drugs and all NSAIDs. In elderly patients the terminal plasma half-life of ketorolac is prolonged and plasma clearance may be reduced. The lower end of the dosage range is recommended.

PRECAUTIONS RELATED TO FERTILITY: The use of TROMIT, as with any drug known to inhibit cyclooxygenases / prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of TROMIT should be considered.

FLUID RETENTION AND EDEMA: Fluid retention, hypertension and edema have been reported with the use of TROMIT and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.

ABUSE/DEPENDENCE: TROMIT is devoid of addictive potential. No withdrawal symptoms have been observed following abrupt discontinuation of TROMIT.

INTERACTIONS WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF INTERACTION
In patients currently receiving ASA or other NSAIDs, the risk of inducing serious NSAID-related adverse events may be increased (**see CONTRAINDICATIONS**). When TROMIT is administered concurrently with oxpentifylline, there is an increased tendency to bleeding (**see CONTRAINDICATIONS**). Decreased plasma clearance and volume of distribution of ketorolac, increased ketorolac plasma concentrations and increased half-life of ketorolac have been reported when TROMIT is administered concurrently with probenecid (**see SPECIAL WARNINGS AND PRECAUTIONS**).
Some prostaglandin synthesis-inhibiting drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity (**see SPECIAL WARNINGS AND PRECAUTIONS**).
Inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis-inhibiting drugs. Cases of increased lithium plasma concentrations during TROMIT Therapy have been reported. Ketorolac tromethamine does not alter digoxin protein binding. In-vitro studies indicate that, at therapeutic concentrations of salicylate (300 mcg/ml), the binding of ketorolac was reduced from approximately 99.2-97.5%, representing a potential two-fold increase in unbound ketorolac plasma concentrations. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac tromethamine protein binding.
Although studies do not indicate a significant interaction between TROMIT and warfarin or heparin, the concurrent use of TROMIT and

therapy that affects hemostasis, including therapeutic doses of anticoagulation therapy (warfarin), prophylactic low-dose heparin (2500-5000 units12-hourly) and dextrans may be associated with an increased risk of bleeding (**see SPECIAL WARNINGS AND PRECAUTIONS**).
TROMIT 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.
Other NSAIDs have been associated with an increased risk of renal impairment when concomitantly administered with ACE inhibitors. Ketorolac may have a similar action by the same mechanism. TROMIT has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.

PREGNANCY AND LACTATION
TROMIT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
TROMIT is contraindicated in labour and delivery because, through its prostaglandin synthesis inhibitory effect if may adversely affect fetal circulation and inhibit uterine contractions thus increasing the risk of uterine hemorrhage (**see CONTRAINDICATIONS**).
TROMIT should be used by nursing mothers only if the potential benefit justifies the potential risk to the fetus.
There was no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of ketorolac tromethamine. Prolongation of the gestation period and/or delayed parturition was seen in the rat. Ketorolac crosses the placenta to the extent of approximately 10%. Ketorolac has been detected in human milk at low concentrations.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of TROMIT. If patients experience these, or other similar undesirable effects, they should exercise caution in carrying out activities that require alertness. Caution is advised when probenecid is administered concurrently, since alterations in the pharmacokinetics of ketorolac have been reported with this combination (**see INTERACTIONS**). 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 (**see INTERACTIONS**).

UNDESIRABLE EFFECTS
The following undesirable effects may occur in patients receiving TROMIT:

GASTROINTESTINAL TRACT: abdominal pain/discomfort, anorexia, constipation, diarrhea, dyspepsia, eructation, flatulence, fullness, gastritis, gastrointestinal bleeding, hematemesis, nausea, esophagitis, pancreatitis, gastrointestinal ulceration, gastrointestinal perforation, stomatitis, vomiting, rectal bleeding, melena.

CENTRAL NERVOUS/MUSCULOSKELETAL SYSTEMS: abnormal dreams, abnormal thinking, anxiety, aseptic meningitis, convulsions, depression, dizziness, drowsiness, dry mouth euphoria, excessive thirst, hallucinations, headache, hyperkinesia, inability to concentrate, Insomnia, myalgia, nervousness, paresthesia, psychotic reactions, sweating, vertigo.

URINARY TRACT AND KIDNEYS: acute renal failure, flank pain (with or without hematuria + azotemia), hemolytic uremic syndrome, hyperkalemia, hyponatremia, increased urinary frequency, urinary retention, Interstitial nephritis, nephrotic syndrome, oligouria, raised serum urea and creatinine.
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 TROMIT.

CARDIOVASCULAR SYSTEM: bradycardia, flushing, hypertension, pallor, palpitations, hypotension, chest pain.

REPRODUCTIVE: Female Infertility.

RESPIRATORY SYSTEM: asthma, dyspnea, pulmonary edema.

HEPATOBILIARY: abnormal liver function tests, hepatitis, cholestatic jaundice, liver failure.

SKIN: exfoliative dermatitis, Lyell's syndrome, macuiopapular rash, pruritus, Stevens-Johnson syndrome, Urticaria.

HYPERSENSITIVITY REACTIONS: anaphylaxis, bronchospasm, flushing rash, hypotension, laryngeal edema, angloedema, anaphylactoid reactions. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

HEMATOLOGICAL: purpura, thrombocytopenia, epistaxis, hematomata, postoperative wound hemorrhage, increased bleeding time,

SPECIAL SENSES: abnormal taste, abnormal vision, tinnitus, hearing loss.

OTHERS: asthenia, edema, injection site reactions, weight gain, fever.

OVER-DOSE
Single overdoses of TROMIT 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 significantly clear ketorolac from the blood stream.

PHARMACOLOGICAL PROPERTIES AND EFFECTS
TROMIT is potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis and it demonstrates minimal anti-inflammatory effect at its analgesic dose.
TROMIT has not known effects on central opioid receptors; 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.
PHARMACOKINETIC PROPERTIES
AMPOULES: Following intramuscular administration, ketorolac tromethamine was rapidly and completely absorbed, a mean peak plasma concentration of 2.2 mcg/ml occurring an average of 50 minutes after a single 30mg 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 single 30mg I.M. dose of ketorolac tromethamine).

Type of patients	Total Clearance (1/h/kg) Mean (range)	Terminal half-life <h) mean (range)
Normal patients (n = 54)	0.023(0.10-0.046)	5.3(3.5-9.2)
Patients with hepatic Impairment (n = 7)	0.029(0.013-0.066)	5.4(2.2-6.9)
Patients with renal impairment (serum creatinine 160-430 umol/l) (n=25)	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)
Healthy elderly Patients (mean age 72) (n = 13)	0.019(0.013-0.034)	7.0(4.7-8.6)

Intravenous administration of a single 10mg dose of ketorolac tromethamine resulted in a mean peak plasma concentration of 2.4 mcg/ml occurring an average of 5.4 minutes after dosing, with an average terminal plasma elimination half-life of 5.1 hours, an average volume of distribution of 0.15 l/kg, and a total plasma clearance of 0.35ml/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 the urine and 6.1 % (mean) in the faces. More than 99% of the ketorolac tromethamine in plasma is protein-bound over a wide concentration range.

PHARMACOKINETICS IN SPECIAL POPULATIONS
THE ELDERLY (≥ 65 YEARS OF AGE): In the elderly the terminal plasma half-life of ketorolac is prolonged compared to young healthy volunteers to an average of 7 hours, ranging from 4.3-8.6 hours. The total plasma clearance may be reduced compared to young healthy volunteers, on average to 0.019 l/h/kg (**see DOSAGE AND ADMINISTRATION and SPECIAL WARNINGS AND PRECAUTIONS**).
RENAL IMPAIRMENT: Elimination of ketorolac is decreased in patients with renal impairment as reflected by a prolonged plasma half-life and reduced total plasma clearance when compared to young healthy subjects. The rate of elimination is reduced roughly in proportion to the degree of renal impairment, except for patients who are severely renally impaired, in whom there is higher plasma clearance of ketorolac than estimated from the degree of renal impairment alone (**see DOSAGE AND ADMINISTRATION and CONTRAINDICATIONS**).

HEPATIC IMPAIRMENT: Patients with impaired hepatic function do not have any clinically important change in ketorolac pharmacokinetics, although there is a statistically significant prolongation of Tmax and terminal phase half-life compared to young healthy volunteers.

PHARMACEUTICAL PARTICULARS
LIST OF EXCIPIENTS:
Ampoules: sodium chloride, ethanol and water for injections.

INCOMPATIBILITIES: TROMIT 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.
TROMIT ampoules are compatible with normal saline, 50% dextrose, Ringer's solution, Ringer-Lactate solution or Plasmalyte solution. Compatibility with other drugs is unknown.

INSTRUCTIONS
Store at 15-25°C. Protect from light and heat. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.
Avoid freezing & injection should not be used if ampoule is leaking, solution is cloudy or contains undissolved matter.

PRESENTATION
Tromit Injection: 5 Ampoules of 1ml

ٹرامِٹ انجکشن
(کیٹوروليک ٹرومیتھامین) یو ایس پی

ہدایات: دوا کو **15** سے **25** ڈگری سینٹی گریڈ پر رکھیں۔ روشنی اور حرارت سے بچائیں۔ تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
منجمد ہونے سے بچائیں۔ انجکشن کے لیک ہونے، دھندلا ہونے یا اس میں غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

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