

TOPADOL®

טופדול®

INJECTION

להזרקה לתוך השריר

### Composition

Each ampoule of 1 ml contains:

#### *Active Ingredient*

Ketorolac tromethamine 30 mg

#### *Other Ingredients*

Alcohol, sodium chloride, water for injection.

### Action

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic, anti-inflammatory, and antipyretic activity. Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally-acting analgesic.

#### *Pharmacodynamics*

Ketorolac tromethamine is not a narcotic agonist or antagonist. Subjects did not show any subjective symptoms or objective signs of drug withdrawal upon abrupt discontinuation of intravenous or intramuscular dosing. Ketorolac tromethamine did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. *In vitro*, ketorolac tromethamine does not bind to opiate receptors. These studies demonstrate that ketorolac tromethamine does not have central opiate-like activity.

Pain relief, following extraction of third impacted molars, is clinically evident when steady state plasma levels exceed 0.3 µg/ml, while side effects are frequent above concentrations of 5 µg/ml. Pain relief is often perceptible in about 10 minutes after ketorolac tromethamine administration, but peak analgesia lags peak plasma levels by 45 to 90 minutes.

#### *Pharmacokinetics*

Ketorolac tromethamine is completely absorbed following intramuscular administration and a mean peak plasma concentration of 2.2 - 3.0 µg/ml occurs on an average of 50 minutes after a single 30 mg dose. The terminal plasma half-life is 3.8 - 6.3 hours in young adults and 4.7 - 8.6 hours in elderly subjects (mean age 72). More than 99% of the ketorolac tromethamine in plasma is protein-bound over a wide concentration range.

The pharmacokinetics of ketorolac tromethamine in man, following single or multiple intramuscular doses, are apparently linear, e.g. plasma levels are approximately proportional to dosage. Steady state plasma levels are achieved after dosing every 6 hours for one day. No changes in clearance occur with chronic dosing. Ketorolac tromethamine, following intravenous and intramuscular administration, displays characteristics of a two-compartment model. In order to minimize the time delay in achieving adequate analgesic effect from the initial dose of a given regimen, a loading dose equal to twice the maintenance dose is recommended.

This is based on the pharmacokinetic principle that when the dosing interval is near the drug's half-life, the target steady-state plasma level is achieved faster if the first dose is twice the maintenance dose.

The primary route of excretion of ketorolac tromethamine and its metabolites is in the urine (mean 91.4%) and the remainder (mean 6.1%) is excreted in the feces.

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).

### *Clinical Studies*

The analgesic efficacy of intramuscularly administered ketorolac tromethamine was investigated in two post-operative pain models: general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were primarily double-blind, single-dose, parallel trial designs, in which ketorolac tromethamine was compared to pethidine or morphine administered intramuscularly to patients with moderate to severe pain at base line. During the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics. Ketorolac tromethamine 30 mg intramuscularly gave pain relief comparable to pethidine 100 mg or morphine 12 mg. The duration of analgesia was longer with ketorolac tromethamine. The percentage of patients who did not re-medicate by 6 hours, i.e., by the end of the studies, was roughly 60% for ketorolac tromethamine 30 mg, as compared to 30% for the two narcotics.

In a multi-dose (10 doses), post-operative (general surgery) double-blind trial of ketorolac tromethamine 30 mg I.M. versus morphine 6 and 12 mg, each drug given on an "as needed" basis, the overall analgesic effect of ketorolac tromethamine 30 mg was in between that of morphine 6 and 12 mg. Ketorolac tromethamine 30 mg caused less drowsiness, nausea and vomiting than morphine 12 mg.

### **Indications**

Intramuscular injection of ketorolac tromethamine is indicated for the short-term management of moderate to severe acute post-operative pain. Maximum duration of treatment is 2 days.

### **Contraindications**

- Patients with known hypersensitivity to ketorolac tromethamine or other NSAIDs, and those in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients), and patients with the complete or partial syndrome of nasal polyps, angioedema, or bronchospasm.
- Patients with a history of peptic ulcer or coagulation disorders.
- Patients with suspected or confirmed gastrointestinal bleedings and/or cerebrovascular bleedings.
- Asthma.
- Dehydration.
- Hypovolaemia from any cause.
- During pregnancy, labor, delivery or breastfeeding.
- Moderate to severe renal impairment.
- Patients with haemorrhagic diathesis.
- Patients who underwent operations having haemorrhagic high risk or incomplete haemostasis.
- Ketorolac, as an NSAID should not be used with other NSAIDs.
- Concomitant use with pentoxifylline.
- Concomitant use with probenecid.
- Concomitant use with lithium salts.
  
- Patients on full anticoagulation therapy; for the concomitant use with prophylactic low-dose heparin (2,500 - 5,000 U 12-hourly) see Precautions and Drug Interactions.
- Children under 16 years of age.

## Warnings

(See also Contraindications).

Anaphylactic reactions occur usually in patients with a history of hypersensitivity to aspirin, other NSAIDs, or ketorolac. They may however also occur in patients without a known previous exposure or hypersensitivity to these agents. Both types of anaphylactic reactions have the potential for being fatal.

Ketorolac tromethamine can cause gastrointestinal irritation, ulcers or bleeding, and should be given under close supervision to patients with a history of gastrointestinal tract disease. Elderly and debilitated patients are most susceptible to these complications, the incidence of which increases with dose and duration of treatment, and most spontaneous reports of fatal gastrointestinal events are in this population.

### *Carcinogenicity, Mutagenicity and Impairment of Fertility*

In animal studies, ketorolac tromethamine was not associated with tumorigenicity or mutagenicity and did not demonstrate teratogenic potential.

### *Use in Pregnancy*

See Contraindications.

### *Use in Labor and Delivery*

See Contraindications.

### *Use in Breastfeeding*

Ketorolac tromethamine appears in human milk, therefore Topadol must not be administered to nursing mothers (see Contraindications).

### *Use in Pediatrics*

Safety and efficacy in children under 16 years of age have not been established (see Contraindications).

### *Use in the Elderly*

Because ketorolac tromethamine is cleared somewhat more slowly in the elderly who are also more sensitive to the renal effects of non-steroidal anti-inflammatory drugs, extra caution and reduced dosages should be used when treating the elderly with Topadol.

## Adverse Reactions

Adverse reaction rates from short-term use of non-steroidal anti-inflammatory drugs are generally from one-half to one-tenth the rates associated with chronic usage. This is also true for ketorolac tromethamine. Physicians using Topadol injection should be alert for the usual complications of NSAID-treatment.

The adverse reactions listed below were reported to be probably related to ketorolac tromethamine in clinical trials in which patients received up to 20 doses of intramuscularly administered ketorolac tromethamine 30 mg, in five days. Reactions are listed under body systems.

### Incidence Greater than 1%

*Body as a whole:* Edema.

*Gastrointestinal:* Nausea\*, dyspepsia\*, gastrointestinal pain\*, diarrhea.

*Central Nervous System:* Drowsiness\*, dizziness, headache, sweating.

Injection site pain was reported by 2% of patients in multidose studies (vs. 5% for morphine control group).

**Note:** \* indicates incidence of reported reactions between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

#### Incidence 1% or less

*Body as a whole:* Asthenia, myalgia.

*Cardiovascular:* Vasodilation, pallor.

*Dermatologic:* Pruritus, urticaria, rash.

*Gastrointestinal:* Constipation, flatulence, gastrointestinal fullness, gastritis, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting.

*Metabolic/Nutritional:* Weight gain.

*Hemic and Lymphatic:* Purpura.

*Central Nervous System:* Dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo.

*Respiratory:* Dyspnea, asthma.

*Special Senses:* Abnormal taste, abnormal vision, tinnitus.

*Urogenital:* Increased urinal frequency, oliguria, hematuria.

The following postmarketing adverse experiences, although rare, have been reported spontaneously for patients who have received ketorolac:

- Acute renal failure, flank pain with or without hematuria and/or azotemia.
- Hypersensitivity reactions such as anaphylaxis, bronchospasm, laryngeal edema, hypotension, flushing and rash.
- Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash.
- Pulmonary edema.
- Gastrointestinal hemorrhage, peptic ulceration, gastrointestinal perforation.
- Postoperative wound hemorrhage, rarely requiring blood transfusion, thrombocytopenia.
- Convulsions, abnormal dreams, hallucinations, hyperkinesia, hearing loss.

### **Precautions**

(See also Contraindications)

#### *General*

The maximum duration of treatment must not exceed 2 days, because adverse events may increase with prolonged usage.

Ketorolac is not an anesthetic agent and 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.

Ketorolac is not recommended in obstetric analgesia.

#### *Renal Effects*

As with other non-steroidal anti-inflammatory drugs that inhibit prostaglandin biosynthesis, elevations of blood urea nitrogen (BUN) and creatinine have been reported in clinical trials with ketorolac tromethamine.

Since ketorolac and its metabolites are excreted primarily by the kidneys, patients with significant impairment of renal function must not receive Topadol unless the expected benefits outweigh the risks. If used in patients with impaired renal function, Topadol dosage should be reduced and renal status should be closely monitored.

In patients with serum creatinine values from 1.9 to 5.0 mg/dl, the rate of ketorolac clearance was reduced to approximately half of normal. The total daily dose of ketorolac should be reduced by half in such patients.

Because of limited experience with more severe degrees of renal impairment, ketorolac is not recommended for patients with serum creatinine levels above 5.0 mg/dl. The disposition of ketorolac tromethamine in dialysis patients has not been studied.

Renal toxicity has been seen 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 a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in renal prostaglandin formation, further decrease in renal blood flow, and may precipitate overt renal failure. Close monitoring of urine output, serum urea and serum creatinine is recommended until the patient is normovolemic.

Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

As with other drugs that inhibit prostaglandin biosynthesis, the following renal abnormalities may also be associated with the use of ketorolac: glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure. Other renal diseases are possible.

#### *Hepatic Effects*

As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials (with the oral formulations of ketorolac tromethamine) in less than 1% of patients.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with Topadol. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Topadol should be discontinued. Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac tromethamine clearance.

#### *Hematological Effects*

Ketorolac tromethamine inhibits platelet aggregation and may prolong bleeding time.

Patients on full anticoagulation therapy (e.g., heparin or dicumarol derivatives), may be at increased risk of bleeding if given ketorolac concurrently. Thus, the benefit should be weighed against this risk.

Patients who have coagulation disorders or are receiving drug therapy that interferes with hemostasis, should be carefully observed when Topadol is administered. Unlike the prolonged effects from aspirin, the inhibition of platelet function by ketorolac disappears within 24 to 48 hours after the drug is discontinued. Ketorolac does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT).

In controlled clinical studies, the incidence of clinically significant post-operative bleeding was 5/1170 (0.4%) compared to 1/570 (0.2%) in the control groups receiving opiates.

In postmarketing experience, postoperative wound hemorrhage has been reported rarely in association with the immediate perioperative use of ketorolac. Therefore, caution should be exercised where strict hemostasis is critical. Specifically in cosmetic plastic surgery, hematomas and other signs of wound hemorrhage have been reported with the use of ketorolac. Physicians should be alert to the pharmacologic

similarity of ketorolac to other non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase.

#### *Fluid Retention and Edema*

Fluid retention and edema have been reported with the use of NSAIDs; therefore, Topadol should be used with caution in patients with cardiac decompensation, hypertension, or similar conditions.

#### *Drug Interactions*

Ketorolac tromethamine is highly bound to human plasma protein (mean 99.2%) and binding is independent of concentration. Because ketorolac tromethamine is a highly potent drug and present in low concentrations in plasma, it would not be expected to displace most other highly protein-bound drugs significantly.

Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide, and piroxicam, did not alter ketorolac tromethamine protein-binding.

*Ketorolac/ Heparin:* In a study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and ketorolac tromethamine did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time; however, inhibition of platelet aggregation by ketorolac, and the potential occurrence of gastrointestinal ulceration or bleeding with prolonged ketorolac administration, may be hazardous to the patients receiving anticoagulant or thrombolytic therapy (see Contraindications).

*Ketorolac/ Salicylate:* In vitro studies indicated that at therapeutic concentrations of salicylate (300 µg/ml) the binding of ketorolac was reduced from approximately 99.2% to 97.5%; hence Topadol should be used with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens.

*Ketorolac/ Other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):* Ketorolac must not be used with other NSAIDs because of the potential for additive side effects (see Contraindications).

*Ketorolac/ Furosemide:* Ketorolac reduces the diuretic response to furosemide in normovolemic healthy subjects by approximately 20%.

*Ketorolac/ Lithium:* Non-steroidal anti-inflammatory drugs have been reported to inhibit renal lithium clearance, leading to an increase in plasma lithium concentrations and potential lithium toxicity (see Contraindications).

*Ketorolac/ Methotrexate:* Concomitant administration of methotrexate and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac on methotrexate clearance has not been studied.

*Ketorolac/ Morphine:* Ketorolac tromethamine has been administered concurrently with morphine in several clinical trials of post-operative pain, without evidence of adverse interactions.

*Ketorolac/ Cefamandole/ Cefoperazone/ Cefotetan/ Moxalactam/ Plicamycin/ Valproic Acid:* These medications may cause hypoprothrombinemia; in addition, plicamycin or valproic acid may inhibit platelet aggregation, and moxalactam may cause irreversible platelet damage. As with other NSAIDs, concurrent use may increase the risk of bleeding because of additive interferences with blood clotting

and/or the potential occurrence of gastrointestinal ulceration or hemorrhage during NSAID therapy.

*Ketorolac/ Probenecid:* Concomitant administration of ketorolac and probenecid decreases the renal clearance of ketorolac, resulting in increased plasma

concentrations and risk of toxicity. Therefore, use of this combination should be avoided (see Contraindications).

*Ketorolac/Pentoxifylline:* Pentoxifylline inhibits platelet aggregation and has also caused prolongation of the prothrombin time and bleeding. Therefore concomitant administration with ketorolac may lead to additive interference with blood clotting (see Contraindications).

## **Dosage and Administration**

*Parenteral drug products should be inspected visually for particle matter and discoloration, prior to administration, whenever solution and container permit.*

*Topadol Injection is to be administered by the intramuscular route.*

Ketorolac tromethamine must not be used in children under 16 years of age (see Contraindications and Warnings).

The maximum duration of treatment must be 2 days, because adverse events may increase with prolonged usage.

The starting dose should be 10 mg, with a subsequent dose of 10-30 mg every 4-6 hours as required. The lowest effective dose should be given. A total daily dose of 90 mg for the non-elderly and 60 mg for the elderly should not be exceeded.

Note: In patients who have received parenteral ketorolac and are converted to oral tablets, a total combined daily dose of all forms of ketorolac tromethamine should not exceed 90 mg for the non-elderly and 60 mg for the elderly.

Ketorolac tromethamine does not interfere with opiate binding and does not exacerbate opiate-related respiratory depression or sedation. Therefore, opiate analgesics (e.g., morphine and pethidine) may be concomitantly used if, in addition to further pain relief, the anxiolytic and/or sedative effects of opiates are needed. When used in association with Topadol, the daily dose of morphine required is much less than the total morphine doses ordinarily required for pain relief following major surgery.

## **Overdosage**

The absence of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy at this time.

At single oral doses greater than 100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales and vomiting were observed.

**Product Registration Number:** 104572603400

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