1. NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name : PANACHE Injection

1.2 Generic Name : Ketorolac Tromethamine Injection USP

1.3 Strength : 30 mg/ml

1.4 Pharmaceutical Form: Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each ml Contains:

Ketorolac Tromethamine USP…….30 mg

Water for injections BP……q.s.

S.No.	Ingredients	Reference	Unit composition (Qunatity/ml)	Functionality
1.	Ketorolac Tromethamine	USP	*31.53 mg	Active Pharmaceutical Ingredient
2.	Absolute Alcohol (Dehydrate)	IH	0.115 ml	Solvent
3.	Sodium Hydroxide Pellets	BP	1.00 mg	For pH adjustment
4.	Hydrochloric Acid	BP	0.0001 ml	For pH adjustment
5.	Sodium Chloride	BP	43.50 mg	Isotonic agent
6.	Water for injections	BP	q.s. to 1 ml	Vehicle

*This quantity has been calculated considering equivalent to its 100% assay on is basis considering the minimum Assay; not less than: 98.5% (ODB) & Maximum LOD not more than 0.5% w/w.

3. PHARMACEUTICAL FORM:

Solution for Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Ketorolac Injection is indicated for the short-term management of moderate to severe acute post-operative pain. Treatment should only be initiated in hospitals. The maximum duration of treatment is 5 days.

4.2 Posology and method of administration

Ketorolac Tromethamine Injection is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over at least 15 seconds. Ketorolac 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, maximum analgesia occurs within one to two hours. Analgesia normally lasts for four to six hours.

Dosage should be adjusted according to the severity of the pain and the patient response. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. 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.

Adult

The recommended initial dose of Ketorolac Injection is 10mg followed by 10 to 30mg every four to six hours as required. In the initial post-operative period, Ketorolac Injection may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90mg for non-elderly and 60mg for the elderly, patients with renal impairment and patients less than 50kg should not be exceeded. The maximum duration of treatment should not exceed two days. The dosage in patients under 50 kg should be reduced.

Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly, and may be required for optimal analgesic effect in the early post-operative period when pain is most severe. Ketorolac does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. When used in association with Ketorolac Injection, 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.
Patients receiving Ketorolac Injection, and oral Ketorolac, should receive a total combined daily dose not exceeding 90mg (60mg for the elderly, patients with renal impairment and patients less than 50kg). 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.

Elderly

For patients over 65 years, the lower end of the dosage range is recommended and a total daily dose of 60mg should not be exceeded. The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children

Safety and efficacy in children have not been established. Therefore, Ketorolac Injection is not recommended for use in children under 16 years of age.

Renal impairment

Ketorolac Injection should not be used in moderate to severe renal impairment and a reduced dosage given in lesser impairment (not exceeding 60mg/day IV or IM).

4.3 Contraindications

- Active peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation
- Active or history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Hypersensitivity to ketorolac trometamol or any of the excipients
- NSAIDS are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs (severe anaphylactic-like reactions have been observed in such patients).
- 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 hemorrhage or incomplete hemostasis and those at high risk of bleeding such as those with hemorrhagic diatheses, including coagulation disorders.
- Patients with complete or partial syndrome of nasal polyps, angioedema or bronchospasm
- Concurrent treatment with aspirin or other NSAIDs including cyclooxygenase 2 specific inhibitors.
- Probenecid or lithium salts
- Moderate or severe renal impairment (serum creatinine> 160 micromole/liter) or in patients at risk for renal failure due to volume depletion or dehydration
- A history of asthma
- Severe heart failure, hepatic failure and renal failure.
- Patients on anti-coagulants including warfarin and low dose heparin (2500 - 5000 units twelve hourly)
- During pregnancy, labor, delivery or lactation.
- Children under 16 years of age.
- Ketorolac is contra-indicated 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 Solution for injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.
- The combination of Ketorolac with oxpentifylline is contraindicated.

4.4 Special warnings and precautions for use

Ketorolac: Epidemiological evidence suggests that ketorolac may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially when used outside the licensed indications and/or for prolonged periods.
Physicians should be aware that in some patient's pain relief might not occur until 30 minutes or more after IV or IM administration.
The use of ketorolac with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided
Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.

Gastro-intestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including ketorolac therapy, at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
A study has shown increased rates of clinically serious GI bleeding in patients < 65 years of age who received an average daily dose of> 90mg ketorolac IM as compared to those patients receiving parenteral opioids.
The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal. This age-related risk of gastrointestinal bleeding and perforation is common to all NSAIDs. Compared to young adults, the elderly have an increased plasma half-life and reduced plasma clearance of ketorolac. A longer dosing interval is advisable.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, including ketorolac, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly. The risk of clinically serious gastrointestinal bleeding is dose dependent. These patients should commence on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. When GI bleeding or ulceration occurs in patients receiving ketorolac, the treatment should be withdrawn.

NSAIDs should be given with care in patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.
Use in patients taking anticoagulants such as warfarin is contraindicated.

As with other NSAIDs the incidence and severity of gastrointestinal complications may increase with increasing dose and duration of treatment with ketorolac. 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 ketorolac. A history of peptic ulcer disease increases the possibility of developing serious gastrointestinal complications during Ketorolac therapy.

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. Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although ketorolac has not shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk for ketorolac. Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ketorolac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking).

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: As with other NSAIDs, ketorolac 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 Ketorolac 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 ketorolac or other NSAIDs may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation or failure. Patients at greatest risk of this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of ketorolac or other non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

As with other drugs that inhibit prostaglandin synthesis, elevations of serum urea, creatinine and potassium have been reported with ketorolac and may occur after one dose.

Patients with impaired renal function: since ketorolac and its metabolites are excreted primarily by the kidney, patients with moderate to severe impairment of renal function (serum creatinine greater than 160 micromol/l) should not receive Ketorolac Injection. Patients with lesser renal impairment should receive a reduced dose of ketorolac (not exceeding 60mg/day IM or IV) and their renal status should be closely monitored.

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 very rarely in association with the use of NSAIDs. Patients appear to be at highest risk of these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Ketorolac trometamol 30mg/ml Solution for Injection should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Precautions related to female fertility: The use of ketorolac, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation for infertility, withdrawal of ketorolac should be considered.

Cardiovascular, Renal and Hepatic Impairment: Caution should be observed 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 an NSAID may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal failure. Patients at greatest risk of this reaction are those who are volume depleted because of blood loss or severe dehydration, patients with impaired renal function, heart failure, liver dysfunction, the elderly and those taking diuretics. Renal function should be monitored in these patients. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state. Inadequate fluid/blood replacement during surgery, leading to hypovolemia, may lead to renal dysfunction, which could be exacerbated when ketorolac is administered. Therefore, volume depletion should be corrected and close monitoring of serum urea and creatinine and urine output is recommended until the patient is normovolaemic. In patients on renal dialysis, ketorolac clearance was reduced to approximately half the normal rate and terminal half-life increased approximately three-fold.

Sodium/fluid retention in cardiovascular conditions and peripheral oedema
Caution is required in patients with a history of hypertension and /or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Fluid retention, hypertension and peripheral oedema has been observed in some patients taking NSAIDs including Ketorolac and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.

Patients with impaired hepatic function: Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac clearance or terminal half-life.
Borderline elevations of one or more liver function tests may occur. These abnormalities may be transient, may remain unchanged, or may progress with continued therapy. Meaningful elevations (greater than three times normal) of serum glutamate pyruvate transaminase (SGPT/ALT) or serum glutamate oxaloacetate transaminase (SGOT/AST) occurred in controlled clinical trials in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, ketorolac should be discontinued.

Anaphylactic (anaphylactoid) reactions
Anaphylactic (anaphylactoid) reactions (including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal oedema and angioedema) may occur in patients with or without a history of hypersensitivity to aspirin other NSAIDs or ketorolac. 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. Therefore, ketorolac should not be used in patients with a history of asthma and in patients with the complete or partial syndrome of nasal polyps, angioedema and bronchospasm.

Hematological 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 (2500 - 5000 units twelve hourly), warfarin and dextran's 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 hemostasis should be carefully observed if ketorolac is administered. In controlled clinical studies, the incidence of clinically significant post-operative bleeding was less than 1%.

Ketorolac inhibits platelet aggregation and prolongs bleeding time. In patients with normal bleeding function, bleeding times were raised, but not outside the normal range of two to eleven minutes. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24 to 48 hours after ketorolac is discontinued.

Post-operative wound hemorrhage has been reported in association with the immediate peri-operative use of ketorolac. Therefore, ketorolac should not be used in patients who have had operations with a high risk of hemorrhage or incomplete hemostasis. Caution should be used where strict hemostasis is critical, e.g. but not limited to cosmetic or day-case surgery, resection of the prostate or tonsillectomy. Hematomata and other signs of wound hemorrhage and epistaxis have been reported with the use of ketorolac. Physicians should be aware of the pharmacological similarity of ketorolac to other non-steroidal anti-inflammatory drugs that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly.

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.

Drug Abuse and Dependence:
Ketorolac is devoid of addictive potential. No withdrawal symptoms have been observed following abrupt discontinuation of ketorolac.

4.5 Interaction with other medicinal products and other forms ofinteractions

Ketorolac is highly bound to human plasma protein (mean 99.2%) and binding is concentration- independent.

The following medicinal products are not to be co-administered with Ketorolac Injection:

NSAIDs/Aspirin: Ketorolac 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 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 is discontinued.

Anticoagulants: Ketorolac injection is contraindicated in combination with anti-coagulants, such as warfarin since co-administration may cause an enhanced anti-coagulant effect. Although studies do not indicate a significant interaction between ketorolac and warfarin or heparin the concurrent use of ketorolac and therapy that affects hemostasis, including therapeutic doses of anticoagulation therapy (warfarin) prophylactic low-dose heparin (2500-5000 units 12- hourly) and dextran's may be associated with an increased risk of bleeding.

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. Cases of increased lithium plasma concentrations during ketorolac therapy have been reported.

Probenecid should not be administered concurrently with ketorolac because of decreased plasma clearance and volume of distribution of ketorolac leading to increases in ketorolac plasma concentrations and half-life.

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 is administered concurrently with oxpentifylline, there is an increased tendency to bleeding.

The following medicinal products in combination with Ketorolac, are to be co-administered with caution:
Diuretics: Ketorolac Solution for injection reduced the diuretic response to furosemide, in normovolaemic 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.

Diuretics and Antihypertensive: 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 nephrotoxicity.

Corticosteroids: As with all NSAIDs, caution should be taken when co-administering with cortico-steroids 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: Ketorolac Tromethamine does not alter digoxin protein binding. *In vitro* studies indicated that at therapeutic concentrations of salicylate (300µg/ml), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma concentrations. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, paracetamol, phenytoin and tolbutamide did not alter ketorolac protein binding. Ketorolac has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain. Oral administration of Ketorolac Tablets after a high-fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac by about 1 hour.

Antacids did not affect the extent of absorption. 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 ketorolac would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.

4.6 Pregnancy and lactation

In view of the known effects of NSAIDs on the fetal cardiovascular system (risk of closure of the ductus arteriosus) ketorolac is contraindicated during pregnancy, labor or delivery.

The safety of ketorolac during human pregnancy has not been established. There was no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of ketorolac. Prolongation of the gestation period and/or delayed parturition were seen in the rat. Congenital abnormalities have been reported in association with NSAID administration in man, however these are low in frequency and do not follow any discemible pattern.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and

embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labor.
- Ketorolac crosses the placenta to the extent of approximately 10%.

Labor and Delivery:

Ketorolac is contraindicated in labor 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 hemorrhage.
There may be increased bleeding tendency in both mother and child.

Lactation:

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 concentrations therefore ketorolac is contra- indicated in mothers who are breast-feeding.

4.7 Effects on ability to drive and use machine

Some patients may experience dizziness, drowsiness, visual disturbances, headaches, vertigo, insomnia or depression with the use of ketorolac. If patients experience these, or other similar undesirable effects, they should not drive or operate machinery.

4.8 Undesirable effects

- Incidence Greater Than 1%

Percentage of incidence in parentheses for those events reported in 3% or more patients

Body as a Whole: edema (4%)

Cardiovascular: hypertension

Dermatologic: pruritus, rash

Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhoea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.

Hemic and Lymphatic: purpura

Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating Injection-site pain was reported by 2% of patients in multi-dose studies.

- Incidence 1% or Less

Body as a Whole: weight gain, fever, infections, asthenia

Cardiovascular: palpitation, pallor, syncope

Dermatologic: urticaria

Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite

Hemic and Lymphatic: epistaxis, anaemia, eosinophilia

Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor

Respiratory: dyspnoea, pulmonary edema, rhinitis, cough

Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss

Urogenital: haematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency

4.9 Overdose

In controlled over dosage, daily doses of 360 mg of Ketorolac Tromethamine Injection given for five (5) days (three times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional over dosage. Dialysis does not significantly clear Ketorolac Tromethamine from the blood stream.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Ketorolac is a potent analgesic agent of the non-steroidal, anti-inflammatory class it is not an opioid and has no known effects on opioid receptors. Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis, demonstrates a minimal anti-inflammatory effect at its analgesic dose.

5.2 Pharmacokinetic properties

Intramuscular

Following intramuscular administration, ketorolac was rapidly and completely absorbed. A mean peak plasma concentration of 2.2µg/ml occurred an average of 50 minutes after a single 30mg dose. Age, kidney and liver function affect terminal plasma half-life and mean total clearance.

Intravenous
Intravenous administration of a single 10mg dose of ketorolac resulted in a mean peak plasma concentration of 2.4µg/ml at an average of 5.4 minutes after dosing. The terminal plasma elimination half-life was 5.1 hours, average volume of distribution 0.15 l/kg, and total plasma clearance 0.35ml/min/kg.
The pharmacokinetics of ketorolac in man following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every six hours for one day. No changes in clearance occurred with chronic dosing. The primary route of excretion of ketorolac and its metabolites is renal: 91.4% (mean) of a given dose being found in the urine and 6.1% (mean) in the faeces. More than 99% of the ketorolac in plasma is protein-bound over a wide concentration range.

5.3 Preclinical safety data

An 18-month study in mice with oral doses of ketorolac trometamol at 2mg/kg/day (0.9 times human systemic exposure at the recommended IM or IV dose of 30mg qid, based on area-under- the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5mg/kg/day (0.5 times the human AUC), showed no evidence of tumourigenicity.

Ketorolac trometamol was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac trometamol did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590µg/ml and at higher concentrations, ketorolac trometamol increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9mg/kg (0.9 times the human AUC) and 16mg/kg (1.6 times the human AUC) of ketorolac trometamol, respectively.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Alcohol USP, Sodium Hydroxide (pellets) BP, Sodium Chloride USP, Water for injections USP.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Store below 30°C. Protect from light & moisture. Do not freeze.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
A printed carton containing PVC tray contains 5 ampoules of amber colour glass of 1 ml with pack insert.

6.6 Special precaution for disposal

There are no special instructions.

7. MARKETING AUTHORIZATION HOLDER

Name	:	Superior Pharmaceuticals Limited
Address	:	9B, Robinson Gbagi Street, Ajao Estate, Lagos.
Phone	:	081-27678822

Name and address of the manufacturer

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