SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ketorolac tromethamine 30 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 30 mg Ketorolac tromethamine

Also contains ethanol 100 mg.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for Injection

Colourless or slightly yellowish solution in amber glass ampoules.

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 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 minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The administration of continuous multiple daily doses of ketorolac intramuscularly or intravenously should not exceed five 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 recommended initial dose of Ketorolac Injection is 10 mg followed by 10 to 30 mg 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 120 mg for non-elderly and 60 mg for the elderly, patients with renal impairment and patients less than 50 kg should not be exceeded. The maximum duration of treatment should not exceed five 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 who are converted to oral Ketorolac, should receive a total combined daily dose not exceeding 120 mg (60 mg for the elderly, patients with renal impairment and patients less than 50 kg). The oral

component should not exceed 40 mg 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 60 mg should not be exceeded (see section 4.4 Special warnings and special precautions for use). 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 2 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 60 mg/day IV or IM) (see section 4.3 Contraindications).

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 haemorrhage or incomplete haemostasis and those at high risk of bleeding such as those with haemorrhagic 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 micromol/l) 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 (see section 4.4)
- patients on anti-coagulants including warfarin and low dose heparin (2500 – 5000 units twelve hourly)
- during pregnancy, labour, delivery or lactation (see section 4.6)
- children under 2 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 (see also sections 4.1, 4.2 and 4.3)

Physicians should be aware that in some patients 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 minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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 (see section 4.2). 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 (see section 4.2).

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 haemorrhage or perforation (see section 4.3), 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 (see below and section 4.5).

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 (see section 4.8).

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 (see section 4.5).

Use in patients taking anticoagulants such as warfarin is contraindicated (see section 4.3).

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 ischaemic 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, hyperlipidaemia, 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 60 mg/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 (see section 4.8).

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 (see section 4.8). 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 tromethamine 30 mg/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 hypovolaemia, 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 (see section 4.3).

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 (see section 4.3).

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 (2500 - 5000 units twelve hourly), warfarin and dextrans 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. 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 haemorrhage 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 haemorrhage or incomplete haemostasis. Caution should be used where strict haemostasis is critical, e.g. but not limited to cosmetic or day-case surgery, resection of the prostate or tonsillectomy.

Haematomata and other signs of wound haemorrhage 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 of interaction

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 (see section 4.3).

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 (see section 4.3).

Although studies do not indicate a significant interaction between ketorolac and warfarin or heparin the concurrent use of ketorolac and therapy that affects haemostasis, including therapeutic doses of anticoagulation therapy (warfarin) prophylactic low-dose heparin (2500-5000 units 12-hourly) and dextrans 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. Coadministration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.

Diuretics and Antihypertensives: 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.

Ciclosporin: As with all NSAIDs caution is advised when ciclosporin is coadministered because of the increased risk of nephrotoxicity.

Corticosteroids: As with all NSAIDs, caution should be taken when coadministering with cortico-steroids because of the increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

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 (see section 4.4) 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 haematological toxicity. There is evidence of an increased risk of haematoma in HIV(+) haemophiliacs 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 (300 µg/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 tromethamine induces or inhibits the hepatic enzymes capable of metabolising 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 Fertility, pregnancy and lactation

Pregnancy:

In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) ketorolac is contraindicated during pregnancy, labour 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 discernible 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 labour.
Ketorolac crosses the placenta to the extent of approximately 10%.
See section 4.4 regarding female fertility.

Labour and Delivery:
Ketorolac is contraindicated in labour and delivery because, through its prostaglandin synthesis inhibitory effect it may adversely affect foetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage. There may be increased bleeding tendency in both mother and child (see section 4.3)

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 machines
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
Post Marketing
The following undesirable effects may occur in patients receiving ketorolac; frequencies of reported events are not known, because they were reported voluntarily from a population of uncertain size.

Gastro-intestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, dyspepsia, abdominal pain/discomfort, haematemesis, stomatitis, dry mouth, oesophagitis, diarrhoea, eructation, constipation, flatulence, fullness, melaena, gastro-intestinal ulceration, rectal bleeding, ulcerative stomatitis, vomiting, pancreatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Blood and Lymphatic system disorders:
Thrombocytopenia, purpura, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Immune System Disorders:
Anaphylaxis, anaphylactoid reactions, anaphylactoid reactions like anaphylaxis, may have a fatal outcome, hypersensitivity reactions such as bronchospasm flushing, rash, hypotension, laryngeal oedema.
These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma and nasal polyps).

Infection:
Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting , fever or disorientation (see section 4.4);

Metabolic and nutrition disorders:
Anorexia, hyponatraemia, hyperkalaemia

Psychiatric disorders:

Abnormal thinking, depression, euphoria, insomnia, anxiety, nervousness, psychotic reactions, abnormal dreams, hallucinations, inability to concentrate, drowsiness, confusion, stimulation.

Nervous system disorders:

Dizziness, headache, paraesthesia, convulsions, abnormal taste, hyperkinesia.

Eye disorders:

Optic neuritis, abnormal vision, visual disturbances

Ear disorders:

Hearing loss, tinnitus, vertigo

Renal and urinary disorders:

Increased urinary frequency, oliguria, acute renal failure, haemolytic uraemic syndrome, flank pain (with or without haematuria +- azotemia), interstitial nephritis, urinary retention, nephrotic syndrome. 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 ketorolac.

Cardiac disorders:

Bradycardia, palpitations, cardiac failure

Vascular disorders:

Flushing, pallor, hypertension, oedema, hypotension, postoperative wound haemorrhage, haematoma.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses) 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 with ketorolac.

Reproductive system and breast disorders:
Female infertility

Respiratory, thoracic and mediastinal disorders:
Dyspnoea, asthma, pulmonary oedema, epistaxis.

Hepatobiliary disorders:
Hepatitis, cholestatic jaundice and liver failure.

Skin and subcutaneous tissue disorders:
pruritus, urticaria, purpura, angiodema, exfoliative dermatitis, maculopapular rash, sweating, bullous reactions including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (very rare). Additionally, erythema multiforme and skin photosensitivity has been observed.

Musculoskeletal and Connective Tissue Disorders:
Myalgia, functional disorders

General Disorders and Administration Site Condition:
Excessive thirst, asthenia, weight gain, fever, injection site reactions and pain, chest pain, malaise, fatigue.

Investigations:

Bleeding time prolonged, serum urea increased and creatinine increased, abnormal liver function, Laboratory Abnormalities
See Section Post Marketing (Undesirable Effects).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Pharmacovigilance Center, Thai FDA.

4.9 Overdose

Symptoms and signs

Single overdoses of Ketorolac 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. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.
Headache, epigastric pain, disorientation, excitation, drowsiness, dizziness, tinnitus and fainting have also been observed.
Rare cases of diarrhoea and occasional convulsions have been reported.
Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment:

Patients should be managed by symptomatic and supportive care following NSAIDs overdose. There are no specific antidotes. Dialysis does not significantly clear ketorolac from the blood stream.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code M01A

Ketorolac is a potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). 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 and it 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 2.2 μg/ml occurred an average of 50 minutes after a single 30 mg dose. Age, kidney and liver function affect terminal plasma half-life and mean total clearance as outlined in the table below (estimated from a single 30mg IM dose of ketorolac).

Type of subjects	Total clearance (l/hr/kg) mean (range)	Terminal half-life (hrs) mean (range)

Normal subjects (n = 54)	0.023 (0.010 - 0.046)	5.3 (3.5 - 9.2)
Patients with hepatic dysfunction (n = 7)	0.029 (0.013 - 0.066)	5.4 (2.2 - 6.9)
Patients with renal impairment (n = 25) (serum creatinine 160 – 430 micromol/l)	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 subjects (n = 13) (mean age 72)	0.019 (0.013 - 0.034)	7.0 (4.7 - 8.6)

Intravenous

Intravenous administration of a single 10mg dose of ketorolac resulted in a mean peak plasma concentration of 2.4 μg/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 0.35 ml/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 tromethamine at 2 mg/kg/day (0.9 times human systemic exposure at the recommended IM or IV dose of 30 mg qid, based on area-under-the-plasma-concentration curve

[AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC), showed no evidence of tumourigenicity.
Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 μg/ml and at higher concentrations, ketorolac tromethamine 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 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, ethanol, sodium hydroxide, hydrochloric acid and water for injections

6.2 Incompatibilities

Ketorolac Injection should not be mixed in a small volume (e.g. in a syringe) with morphine sulfate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation of ketorolac will occur.
It is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmacyte solutions. Compatibility of Ketorolac Injection with other drugs is unknown.

6.3 Shelf life

Two years

6.4 Special precautions for storage

Do not store above 30°C. Keep container in the outer carton and protect from light.

6.5 Nature and contents of container

USP type I colorless and transparent ampoule.

One pack size (box) contains 10, 15, 20, 25 or 50 Amp/box.

6.6 Special precautions for disposal

There are no special instructions.

7 MARKETING AUTHORISATION HOLDER

American Taiwan Biopharm Co., Ltd.

No. 1, Eastwater Building, 16th Floor, Vibhavadi-Rangsit 5, Vibhavadi-Rangsit road, Chom Phon, Chatuchak, Bangkok, 10900

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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