Summary of Product Characteristic

1. Name of the Medicinal Product

1.1 Product Name

Kerolac–30

1.2 Strength

Each mL contains:- Ketorolac tromethamine 30 mg

1.3 Pharmaceutical Dosage Form

Solution for injection

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Ketorolac tromethamine

2.2 Quantitative Declaration:

Each mL contains:- Ketorolac tromethamine 30 mg

3. Pharmaceutical Form

Clear, colorless to slightly yellow sterile solution for injection

4. Clinical Particulars

4.1 Therapeutic indications

Kerolac–30 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 two days.

4.2 Posology and method of administration

Kerolac–30 is for administration by intramuscular or bolus intravenous injection.

Bolus intravenous doses should be given over no less than 15 seconds. Kerolac–30 should not be used for epidural or spinal administration. The time to onset of analgesic effect following both IV and IM administration is similar and is approximately 30 minutes, with maximum analgesia occurring within one to two hours. The median duration of analgesia is generally four to six hours. Dosage should be adjusted according to the severity of the pain and the patient response. 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. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

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, Kerolac–30 may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90 mg for non-elderly and 60 mg for the elderly, renally-impaired patients and patients less than 50 kg should not be exceeded. The maximum duration of treatment should not exceed two days.

Reduce dosage in patients under 50 kg.

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 Kerolac–30 IM/IV, 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. For patients receiving parenteral Kerolac–30, and who are converted to Ketorolac Trometamol oral tablets, the total combined daily dose should not exceed 90 mg (60 mg for the elderly, renally impaired patients and patients less than 50 kg) and 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.

Older People

The older people are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. A total daily dose of 60 mg should not be exceeded.

Children

Safety and efficacy in children have not been established. Therefore, Kerolac–30 is not recommended for use in children under 16 years of age.

Renal impairment

Contraindicated in moderate to severe renal impairment; reduce dosage in lesser impairment (not exceeding 60 mg/day IV or IM).

4.3 Contraindication

Ketorolac is contraindicated in patients with previously demonstrated hypersensitivity to Ketorolac, any of its excipients, or other NSAIDs and patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients). Such reactions have included asthma, rhinitis, angioedema, or urticaria.

Ketorolac is also contraindicated in

- those with a history of asthma
- children under 16 years of age.

Ketorolac is contraindicated in patients with active or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). As with other NSAIDs, Ketorolac is contraindicated in patients with severe heart failure, hepatic failure and renal failure.

Ketorolac is contraindicated in patients with moderate or severe renal impairment (serum creatinine >160 μ mol/l) or in patients at risk for renal failure due to volume depletion or dehydration.

Ketorolac is contraindicated in pregnancy, labour, delivery or lactation.

Ketorolac is contraindicated as prophylactic analgesia before surgery due to inhibition of platelet aggregation and is contraindicated intra-operatively because of the increased risk of bleeding.

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.

It is also contraindicated in patients on anticoagulants, including warfarin and low dose heparin (2500 - 5000 units 12 hourly).

Ketorolac is contraindicated in patients currently receiving ASA or other NSAIDs (including cyclooxygenase-2 selective inhibitors).

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. Concurrent treatment with ketorolac and probenecid or lithium salts is contraindicated.

Ketorolac is contraindicated in patients with the complete or partial syndrome of nasal polyps, angioedema or bronchospasm.

4.4 Special warning and precautions for use

Thai FDA Mandatory Warning

1. Contraindicated in patients with hypersensitivity to Ketorolac or patients in whom aspirin or other NSAIDs induce acute allergic reactions; asthma, urticaria, or rhinitis.
2. Third trimester of pregnancy should be avoided unless prescribed by a doctor.
3. Contraindicated in patients with gastrointestinal bleeding or perforation.
4. Contraindicated in patients with severe hepatic failure and renal failure.
5. Contraindicated in patients with dengue fever.
6. Ketorolac could increase the risk of gastrointestinal ulceration or bleeding.
7. Ketorolac could increase the risk of cerebrovascular and cardiovascular disease, especially when receiving prolonged high-dose treatment.
8. Ketorolac may adversely affect fluid retention. Therefore, it should be used with caution in patients with heart disease and impaired renal function.
9. Caution is required in patients with hypertension or elderly.
10. Ketorolac affects platelet aggregation. Therefore, it should be avoided in patients with suspected dengue or disorders of platelet aggregation.

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 patients pain relief may not occur until upwards of 30 minutes 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 lowest effective dose for the shortest duration necessary to control symptoms.

Gastrointestinal ulceration, bleeding and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs including ketorolac therapy, at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

In a non-randomised, in-hospital post-marketing surveillance study, increased rates of clinically serious GI bleeding were seen in patients < 65 years of age who received an average daily dose of > 90 mg 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. Debilitated patients seem to tolerate ulceration or bleeding less well than others. Most of the fatal gastrointestinal events associated with non-steroidal anti-inflammatory drugs occurred in the elderly and/or debilitated patients. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, including Ketorolac IV, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. The risk of clinically serious gastrointestinal bleeding is dose dependent. These patients should commence treatment 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. 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.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease, (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. 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 IV, treatment should be withdrawn.

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 IV. 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 IV. A history of peptic ulcer disease increases the possibility of developing serious gastrointestinal complications during Ketorolac therapy.

Haematological effects:

Patients with coagulation disorders should not receive Kerolac–30. Patients on anticoagulation therapy may be at increased risk of bleeding if given Kerolac–30 concurrently. The concomitant use of ketorolac and prophylactic low dose heparin (2500 - 5000 units 12-hourly) and dextrans has not been studied extensively and may also be associated with an increased risk of bleeding. Patients already on anticoagulants 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 Kerolac–30 is administered. In controlled clinical studies, the incidence of clinically significant postoperative 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.

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 for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Kerolac–30 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.

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.

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) 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 treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

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 Kerolac–30 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.

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 renal 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 trometamol and may occur after one dose.

Patients with impaired renal function: Since ketorolac trometamol 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 Kerolac–30. 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.

Use in patients with impaired liver 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 3 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, Kerolac–30 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 IV. 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 be used with caution in patients with a history of asthma and in patients with the complete or partial syndrome of nasal polyps, angioedema and bronchospasm.

Precautions related to fertility

The use of Kerolac–30, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of fertility, withdrawal of Kerolac–30 should be considered.

Fluid retention and oedema

Fluid retention, hypertension and oedema have been reported with the use of Ketorolac and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.

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.

Pediatric Use:

Ketorolac given parenterally is not recommended in children younger than 2 years of age.

Drug Abuse and Dependence

Ketorolac is devoid of addictive potential. No withdrawal symptoms have been observed following abrupt discontinuation of Ketorolac IV.

4.5 Interaction with other medicinal products and other forms of interactions

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 Kerolac–30:

Kerolac–30 should not be used with other ASA or other NSAIDs including cyclooxygenase-2 selective inhibitors as the risk of inducing serious NSAID-related adverse events may be increased.

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.

Kerolac–30 is contraindicated in combination with anti-coagulants, such as warfarin since co-administration of NSAIDS and anticoagulants 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 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.

Inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis-inhibiting drugs. Cases of increased lithium plasma concentrations during Ketorolac therapy have been reported.

Probenecid should not be administered concurrently with ketorolac because of increases in ketorolac plasma concentrations and half-life.

NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

The following medicinal products in combination with Kerolac–30 are to be co-administered with caution:

As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastro-intestinal ulceration or bleeding.

There is an increased risk of gastrointestinal bleeding when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

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

Some prostaglandin synthesis-inhibiting drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.

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 twofold increase in unbound ketorolac plasma concentrations. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac protein binding.

Ketorolac Solution for injection reduced the diuretic response to furosemide in normovolemic healthy subjects by approximately 20% so particular care should be taken in patients with cardiac decompensation.

Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.

As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when coadministered with cardiac glycosides.

Ketorolac has been shown to reduce the need for concomitant opioid analgesia when it is given for the relief of postoperative pain.

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.

NSAIDs given with zidovudine increase the risk of haematological toxicity. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

There is no evidence in animal or human studies that ketorolac trometamol induces or inhibits the hepatic enzymes capable of metabolising itself or other drugs. Hence Kerolac–30 would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.

4.6 Fertility, Pregnancy and lactation

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 Kerolac–30 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%.

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.

Nursing Mothers:

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 contraindicated in mothers who are breast-feeding.

4.7 Effects on ability to drive and use machine

Some patients may experience dizziness, drowsiness, fatigue, visual disturbances, headaches, vertigo, insomnia or depression with the use of Kerolac–30. If patients experience these, or other similar undesirable effects, patients should not drive or operate machinery.

4.8 Undesirable effects

Post Marketing

The following undesirable effects may occur in patients receiving Ketorolac IV; 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. Nausea, vomiting, diarrhoea, constipation, dyspepsia, abdominal pain / discomfort, melaena, haematemesis, stomatitis, ulcerative stomatitis, eructation, flatulence, oesophagitis, gastrointestinal ulceration, rectal bleeding, pancreatitis, dry mouth, fullness, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

Infection: meningitis aseptic. (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.

Blood and Lymphatic System Disorders: thrombocytopenia

Additionally, purpura, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia have been observed.

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).

Metabolic and Nutrition Disorders: anorexia, hyperkalaemia, hyponatraemia.

Psychiatric Disorders: abnormal thinking, depression, insomnia, anxiety, nervousness, psychotic reactions, abnormal dreams, hallucinations, euphoria, concentration ability impaired, drowsiness. Confusion and stimulation have been observed.

Nervous system disorders: headache, dizziness, convulsions, paresthesia, hyperkinesias, taste abnormality.

Eye Disorders: abnormal vision, visual disturbances, optic neuritis.

Ear Disorders: tinnitus, hearing loss, vertigo.

Renal and Urinary Disorders: acute renal failure, increased urinary frequency, interstitial nephritis, nephrotic syndrome, urinary retention, oliguria, haemolytic uremic syndrome, flank pain (with or without haematuria +- azotemia). 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 IV.

Cardiac Disorders: palpitations, bradycardia, cardiac failure.

Vascular disorders: hypertension, hypotension, haematoma, flushing, pallor, postoperative wound haemorrhage.

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: asthma, dyspnoea, pulmonary oedema. Additionally, epistaxis has been observed.

Hepatobiliary Disorders: hepatitis, cholestatic jaundice, liver failure.

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, maculopapular rash, pruritus, urticaria, purpura, angioedema, 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 disorder.

General Disorders and Administration Site Condition: excessive thirst, asthenia, oedema, injection site reactions and pain, fever, chest pain. Additionally, malaise, fatigue and weight gain has been observed.

Investigations: bleeding time prolonged, serum urea increased, creatinine increased, abnormal liver function tests

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

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, acetic acid derivatives and related substances. ATC code M01AB15

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

IM: Following intramuscular administration, ketorolac trometamol was rapidly and completely absorbed, a mean peak plasma concentration of 2.2μ g/ml occurring an average of 50 minutes after a single 30 mg dose. The influences of age, kidney and liver function on terminal plasma half-life and mean total clearance are outlined in the table below (estimated from a single 30 mg IM dose of ketorolac).

Type of subjects	**Total clearance (I/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)

IV: Intravenous administration of a single 10 mg dose of ketorolac trometamol resulted in a mean peak plasma concentration of 2.4μ g/ml occurring an average of 5.4 minutes after dosing, with a terminal plasma elimination half-life of 5.1 hours, an average volume of distribution of 0.15 l/kg, and a total plasma clearance of 0.35ml/min/kg.

The pharmacokinetics of ketorolac 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 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 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 1590μ g/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 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac trometamol, respectively.

6. Pharmaceutical Particulars

6.1 List of excipients

Ethanol

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Kerolac–30 should not be mixed in a small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride as precipitation of ketorolac will occur.

It is compatible with 0.9% normal saline, 5% dextrose, Ringer's and lactated Ringer's solution.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30 °C and protect from light.

6.5 Nature and contents of container

1 mL Amber glass vial (Type I) with aluminium flip-off/Chlorobutyl rubber and 1 mL Amber glass ampoule (Type I) packed or unpacked in a box of 1, 5, 10, 12, 20, 25, 50 and 100 vials/ampoules.

6.6 Special precautions for disposal and other handling

After opening the container, the contents should be used immediately and should not be stored for a subsequent. Parenteral drug should be inspected visually for particle matter and discoloration prior to administration, whenever solution and container permit.

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

1A 15209/63 (NG)

9. Date of authorization

24 December, 2020

10. Date of revision of the text

31 August, 2023