1.3.1 Summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
KETOLAC Ampoules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2 ml ampoule contains 30 mg Ketorolac Tromethamin.

For a full list of excipients see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

Very pale-yellow clear solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
KETOLAC 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 2 days.

4.2 Posology and method of administration
Ketolac is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over at least 15 seconds. Ketolac 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 Ketolac 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.

Adults:
The recommended initial dose of Ketolac is 10 mg followed by 10 to 30 mg every four to six hours as required. In the initial post-operative period, Ketolac 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, patients with renal impairment and patients less than 50 kg 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. Ketolac does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. When used in association with Ketolac 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 Ketolac, and who are converted to oral Ketolac, should receive a total combined daily dose not exceeding 90 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. 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, Ketolac is not recommended for use in children under 16 years of age.

Renal impairment:

Ketolac 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).

4.3 Contraindications

- Active or previous peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation (two or more distinct episodes of proven ulceration or bleeding).

- Active or history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.

- Hypersensitivity to ketorolac tromethamine 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).

- Ketolac 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.

- Patients on anti-coagulants including warfarin and low dose heparin (2500 - 5000 units twelve hourly).

- During pregnancy, labour, delivery or lactation.

- Children under 16 years of age.

- Ketolac 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.

- Ketolac is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

- The combination of Ketolac 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 patients pain relief might not occur until 30 minutes or more after IV or IM administration.

Undesirable effects may be minimized by using the lowest 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 > 90 mg Ketolac 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, 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 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 in 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 Ketolac, the 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 Ketolac. 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 Ketolac. A history of peptic ulcer disease increases the possibility of developing serious gastrointestinal complications during Ketolac 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, Ketolac 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 Ketolac 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 Ketolac Injection. Patients with lesser renal impairment should receive a reduced dose of ketolac (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.

Dermatological:
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. Ketolac 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 Ketolac, 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 Ketolac 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. 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.

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 and oedema
Fluid retention, hypertension and oedema have been reported with the use of Ketolac 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, Ketolac 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 Ketolac. 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, Ketolac 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.

Haematological effects:

Patients with coagulation disorders should not receive ketorolac. Patients on anti-coagulation therapy may be at increased risk of bleeding if given Ketolac concurrently. The concomitant use of Ketolac 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 Ketolac. Patients who are receiving other drug therapy that interferes with haemostasis should be carefully observed if Ketolac is administered. In controlled clinical studies, the incidence of clinically significant post-operative bleeding was less than 1%.

Ketolac 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 Ketolac is discontinued.

Post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of Ketolac. Therefore, Ketolac 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.

Pediatric Use:

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

Drug Abuse and Dependence:

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

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 Ketolac Injection:

NSAIDs/Aspirin: Ketolac 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: Ketolac 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 Ketolac is discontinued.

Anticoagulants: Ketolac 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 Ketolac 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 increased plasma lithium concentration with some prostaglandin synthesis-inhibiting drugs, and potential lithium toxicity.

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

The following medicinal products in combination with Ketolac, are to be co-administered with caution:

Diuretics: Ketolac 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 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.

Ketolac and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of beta-blockers and may increase the risk of renal impairment when administered concurrently with ACE inhibitors, particularly in volume depleted patients.

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 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 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 (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.

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 Ketolac would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.

4.6 Pregnancy and lactation

Pregnancy:

The safety of Ketolac during human pregnancy has not been established. There is no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of Ketolac.

Prolongation of the gestation period and/or delayed parturition was 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. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), Ketolac is contraindicated during pregnancy, labour or delivery. The onset of labour may be delayed and the duration increased, with an increased bleeding tendency in both mother and child.

Ketolac crosses the placenta to the extent of approximately 10%.

Labour and Delivery:

Ketolac 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.

Lactation

Ketolac and its metabolites have been shown to pass into the foetus and milk of animals. Ketolac has been detected in human milk at low levels therefore, Ketolac 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 Ketolac. If patients experience these, or other similar undesirable effects, they should not drive or operate machinery.

4.8 Undesirable effects

The following undesirable effects may occur in patients receiving Ketolac; 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, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, dyspepsia, gastro-intestinal pain, abdominal pain/discomfort, haematemesis, gastritis, dry mouth, oesophagitis, diarrhoea, eructation, constipation, flatulence, fullness, melaena, non-peptic gastro-intestinal ulceration, rectal bleeding, ulcerative stomatitis, vomiting, haemorrhage, perforation, pancreatitis, exacerbation of colitis and Crohn's disease have been reported following administration.

Blood and Lymphatic system disorders:

Thrombocytopenia, purpura, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Immune System Disorders:

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis, anaphylactoid reactions (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, (c) assorted skin reactions. Other reactions include hypotension and flushing. Such reactions may occur in patients with or without known sensitivity to Ketolac or other non-steroidal anti-inflammatory drugs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

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.

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 Ketolac.

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 Ketolac has not shown to increase thrombotic events, such as myocardial infarction, there are insufficient data to exclude such a risk with Ketolac.

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, skin photosensitivity, Lyell's syndrome including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (very rare) and erythema multiforme. Skin photosensitivity.

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.

4.9 Overdose
Doses of 360 mg given intramuscularly over an eight hour interval for five consecutive days have caused abdominal pain and peptic ulcers that have healed after discontinuation of dosing. Two patients recovered from unsuccessful suicide attempts. One patient experienced nausea after 210 mg ketorolac, and the other hyperventilation after 300 mg ketorolac.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Ketorolac tromethamine is a non-narcotic analgesic. It is a non-steroidal anti-inflammatory agent that exhibits anti-inflammatory and weak antipyretic activity.

Ketorolac tromethamine inhibits the synthesis of prostaglandins and is considered a peripherally acting analgesic. It does not have known effect on opiate receptors.

No evidence of respiratory depression has been observed after administration of Ketorolac tromethamine in controlled clinical trials. Ketorolac tromethamine does not cause pupil constriction.

5.2 Pharmacokinetic properties
<u>Intramuscular</u>
Following intramuscular administration, ketorolac tromethamine was rapidly and completely absorbed. A mean peak plasma concentration of 2.2µ g/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 as outlined in the table below (estimated from a single 30 mg 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 10 mg dose of ketorolac tromethamine 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 9mg/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

Ethyl Alcohol.

Sodium Chloride.

Sodium Hydroxide.

Water for Injection.

6.2 Incompatibilities

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

It is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmacyte solutions. Compatibility of Ketolac Ampoules with other drugs is unknown.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at temperature not exceeding 30°C, in original package.

6.5 Nature and contents of container

A chromo-duplex carton box containing a patient leaflet and a white opaque plastic drawer (of 5 amber glass ampoules, each of 2 ml).

6.6 Special precautions for disposal

Not special requirements.

7. MARKETING AUTHORISATION HOLDER

AMRIYA PHARM. IND.
Amriya, Alexandria-Cairo Desert Road, Km 25,
Alexandria- Egypt.

8. MARKETING AUTHORISATION NUMBER(S)

19679/2011.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/03/2011.

10. DATE OF REVISION OF THE TEXT

February 2019.