AUSTRALIAN PRODUCT INFORMATION

KETORAL

(ketorolac trometamol) solution for injection

Ketorolac trometamol is a potent NSAID analgesic and the resulting NSAID related adverse effects can be serious, e.g. gastrointestinal haemorrhage, surgical haemorrhage and renal impairment. Increasing the dose of ketorolac trometamol beyond the recommendations in the product information will not provide better efficacy but will result in increasing risk of developing serious adverse effects.

1 NAME OF THE MEDICINE

Ketorolac trometamol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KETORAL contains 30 mg/1 mL of ketorolac trometamol as the active ingredient.

Excipients with known effect: alcohol as 12.3% v/v ethanol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

KETORAL is a clear, slightly yellow sterile solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term management of moderately severe, acute pain following surgical procedures. The total duration of ketorolac trometamol use should not exceed five days.

It is recommended that parenteral ketorolac be used in the immediate postoperative period. Patients can then be converted to an oral formulation (dependent on their analgesic needs) (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Conversion from Parenteral to Oral Therapy).

The total period of treatment utilising the oral and/or intramuscular route of administration is not to exceed five days.

General

Ketorolac trometamol is not recommended for use as an obstetric preoperative medication or for obstetric analgesia because it has not been adequately studied for use in these circumstances and because of the known effects of drugs that inhibit prostaglandin biosynthesis on uterine contraction and fetal circulation. There is no satisfactory evidence for the use of ketorolac trometamol in acute exacerbations of chronic painful inflammatory conditions (e.g. rheumatoid arthritis or osteoarthritis).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. The lowest effective dose should be used for the shortest possible time in all patient populations.

Opiate analgesics (e.g. morphine and pethidine) may be used concomitantly and may be required for optimum analgesic effect in the early postoperative period when pain is most severe, or when the anxiolytic effects and/or sedative effects of opiates are desired.

Ketorolac trometamol has been administered with morphine in several clinical trials of postoperative pain without evidence of adverse interactions. Ketorolac trometamol does not exacerbate opioid related respiratory

depression or sedation. When used in association with ketorolac trometamol administered intramuscularly, the daily dose of opioid is usually less than that which is normally required.

Hypovolaemia should be corrected prior to administration of ketorolac trometamol. The intramuscular injection should be given slowly and deeply into the muscle. The administration of ketorolac trometamol should not exceed five days because adverse events may increase with prolonged usage.

Use in one patient on one occasion only. Discard any residue.

Intramuscular

Adults (< 65 years)

The usual recommended initial dose is 10 to 30 mg followed by 10 to 30 mg every four to six hours up to a maximum daily dose of 90 mg.

Elderly (greater than or equal to 65 years)

An initial dose of 10 to 15 mg followed by 10 to 15 mg every four to six hours up to a maximum daily dose of 60 mg.

Pregnancy

See Section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

Mild Renal Impairment

If used in patients with mildly impaired renal function (serum creatinine values in males: 130 to < 180 micromol/L; in females: 120 to < 180 micromol/L) the lower end of the ketorolac trometamol intramuscular dosage range should be used. The total daily dose should not exceed 60 mg.

Ketorolac trometamol is contraindicated in patients with more severe degrees of renal impairment (see Section 4.3 CONTRAINDICATIONS).

Cardiovascular

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Other

For patients under 50 kg in bodyweight or for patients with less severe pain, the lower end of the ketorolac trometamol intramuscular dosage range is recommended. The total daily dose should not exceed 60 mg.

Conversion from Parenteral to Oral Therapy

For patients receiving ketorolac trometamol intramuscularly, and who are converted to ketorolac trometamol tablets, the total combined daily dose should not exceed 90 mg (60 mg for the elderly, patients with mild renal impairment and patients weighing less than 50 kg) and the oral component should not exceed 40 mg (30 to 40 mg for the elderly) on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible.

4.3 CONTRAINDICATIONS

Severe heart failure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Heart Failure).

Undergoing treatment of perioperative pain in setting of coronary artery surgery (CABG).

Dehydration or hypovolaemia from any other cause.

With severe hepatic impairment.

Moderate or severe renal impairment (serum creatinine > 180 micromol/L) or in patients at risk of renal failure due to volume depletion or dehydration (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Renal Impairment).

Active or a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Gastrointestinal Effects).

A history of haemorrhagic diatheses, including coagulation disorders (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Haematological Effects).

Surgery with a high risk of haemorrhage or incomplete haemostasis; and those at high risk of bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Haematological Effects).

Suspected or confirmed cerebrovascular (intracranial) bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Haematological Effects).

Patients on full anticoagulation therapy (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Receiving aspirin, other NSAIDS, pentoxifylline, probenecid or lithium (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Hypersensitivity to ketorolac trometamol or other NSAIDs, and patients in whom aspirin or other prostaglandin synthetase inhibitors induce allergic reactions. Severe anaphylactic-like reactions have been observed in such patients. If such symptoms occur during therapy, treatment should be discontinued (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Anaphylactic Reactions).

Individuals with the complete or partial syndrome of nasal polyps, angioedema or bronchospasm. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Anaphylactic Reactions).

A history of asthma (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Anaphylactic Reactions).

Prior history of Stevens-Johnson syndrome or vesicular bullous rash (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Severe Skin Effects and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Neuraxial (epidural or intrathecal) administration due to the alcohol content of the solution for injection.

Prophylactic administration before major surgery, due to inhibition of platelet aggregation; and intraoperatively because of the increased risk of bleeding.

Use in pregnancy, labour, delivery or lactation (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy and Use in Lactation)

Children under 16 years of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular Thrombotic Events

Observational studies have indicated that nonselective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse

cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Although ketorolac trometamol has not been shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk for ketorolac.

Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention, cardiac decompensation, heart failure, hypertension or similar conditions.

Gastrointestinal Effects

Ketorolac trometamol can cause gastrointestinal irritation, ulcers, perforation or bleeding, which can be fatal, at any time, with or without warning symptoms or a previous history of serious gastrointestinal events.

Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for three to six months and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal effect at some time during the course of therapy. However, even short-term therapy is not without risk.

The risk of gastrointestinal bleeding, ulceration or perforation increases with dose and duration of treatment; in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation; in the elderly; and in those with a history of smoking or alcoholism. Caution is advised in these patients and treatment should commence on the lowest dose available. Combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients.

Elderly and debilitated individuals are more susceptible to gastrointestinal complications (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Elderly for dosage reductions in this patient group). Most reports of fatal gastrointestinal effects are in this population. NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrointestinal ulceration or bleeding, such as NSAIDs, oral corticosteroids; anticoagulants such as warfarin; selective serotonin reuptake inhibitors (SSRIs); or antiplatelet agents such as aspirin, as these combinations may increase the risk of serious gastrointestinal adverse effects (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients.

Prescribers should warn patients about the signs and symptoms of serious gastrointestinal toxicity. Patients administered ketorolac trometamol should be instructed to advise their doctor immediately if they experience any unusual abdominal symptoms (especially gastrointestinal bleeding). Ketorolac trometamol should be discontinued, appropriate treatment instituted, and the patient closely monitored.

In a non-randomised, in hospital post-marketing surveillance study, increased rates of clinically serious gastrointestinal bleeding were seen in patients 65 years of age and under who received an average daily dose of greater than ketorolac trometamol 90 mg administered IM as compared to those patients receiving parenteral opioids.

Haematological Effects

Ketorolac trometamol inhibits platelet aggregation and may prolong bleeding time. Unlike the prolonged effects from aspirin, the inhibition of platelet function by ketorolac trometamol resolves within 24 to 48 hours after the medicine is discontinued. Ketorolac trometamol does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, the incidence of clinically significant postoperative bleeding was 5/1,170 (0.4%) compared to 1/570 (0.2%) in the control groups receiving opiates.

The use of ketorolac trometamol in patients who have coagulation disorders should be undertaken very cautiously, and those patients carefully monitored. Patients on anticoagulation therapy (e.g. heparin or warfarin) may be at increased risk of bleeding if given ketorolac trometamol concurrently (see Section 4.3 CONTRAINDICATIONS). The concomitant use of ketorolac trometamol and prophylactic low dose heparin has not been studied extensively and may also be associated with an increased risk of bleeding. Concomitant administration of dextrans may also increase the risk of postoperative bleeding. Patients receiving other medicines that affect haemostasis should be carefully observed if ketorolac trometamol is administered (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In post-marketing experience, postoperative wound haemorrhage has been reported in association with the immediate perioperative use of IM ketorolac trometamol. Therefore, ketorolac trometamol should not be used in patients who have had surgery with a high risk of haemorrhage or incomplete haemostasis. Caution should be used where strict haemostasis is critical, e.g. in cosmetic or day care surgery, resection of the prostate or tonsillectomy. Haematomata, other signs of wound haemorrhage and epistaxis have been reported with the use of ketorolac. Doctors should be aware of the pharmacological similarity of ketorolac trometamol to other NSAIDs that inhibit cyclooxygenase and the risk of bleeding, particularly in the elderly.

Severe Skin Effects

NSAIDs may very rarely cause serious cutaneous adverse effects such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) and toxic epidermal necrolysis (TEN), which can be fatal and occur without warning. These serious adverse effects are idiosyncratic and are independent of dose or duration of use.

Patients should be advised of the signs and symptoms of serious skin effects and to consult their doctor at the first appearance of a skin rash or other sign of hypersensitivity.

DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue NSAID and evaluate the patient immediately.

Injection Site Effects

Ketorolac trometamol injection administered IM has produced pain at the injection site in 2 to 4% of patients. Ecchymosis, bruising, haematoma and tingling at the injection site have rarely been reported. Adverse local effects may be minimised by applying pressure at the injection site for 15 to 30 seconds after administration.

There has been no evidence (e.g. alterations in serum creatine kinase (CK) or creatine phosphokinase (CPK) concentrations) of substantial adverse muscular tissue effects following single or multiple IM injections of ketorolac trometamol.

Anaphylactic Reactions

Anaphylactic (anaphylactoid) reactions (including, but not limited to, anaphylaxis, bronchospasm, flushing, rash, hypotension, laryngeal oedema and angioedema) may occur in individuals with or without a history of hypersensitivity to aspirin, other NSAIDs or ketorolac trometamol. 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 trometamol 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.

Special Senses

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ketorolac trometamol should have an ophthalmological examination.

Drug Abuse and Physical Dependence

Ketorolac trometamol is not a narcotic agonist or antagonist. Subjects did not show any subjective symptoms or objective signs of drug withdrawal upon abrupt discontinuation of IM dosing. Ketorolac trometamol did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action (hot plate and tail withdrawal test). In vitro ketorolac trometamol does not bind to opiate receptors. These studies demonstrate that ketorolac trometamol does not have central opiate-like activity.

General

Undesirable effects may be minimised by using the lowest minimum effective dose for the shortest duration necessary to control symptoms (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Ketorolac trometamol is not an anaesthetic agent and possesses no sedative or anxiolytic properties, therefore, it is not recommended as a preoperative or intraoperative medication for the support of anaesthesia when these effects are required. Ketorolac trometamol IM should not be used for spinal or epidural administration. Ketorolac trometamol IM contains ethanol 10% (see Section 4.3 CONTRAINDICATIONS). The total duration of ketorolac trometamol treatment should not exceed five days.

Use in Hepatic Impairment

As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged or may be transient with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (three times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials (with the oral formulation of ketorolac trometamol) in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash), ketorolac trometamol should be discontinued.

Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac trometamol clearance. Studies to assess the pharmacokinetics of ketorolac trometamol in patients with active hepatitis or cholestasis have not been done. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity.

A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms), or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic effects while on therapy with ketorolac trometamol.

Use in Renal Impairment

As with other NSAIDs that inhibit prostaglandin biosynthesis, elevations of serum urea, nitrogen, potassium and creatinine have been reported in clinical trials with ketorolac and can occur after one dose. Ketorolac trometamol and its metabolites are eliminated primarily by the kidneys which, in patients with reduced

creatinine clearance, will result in diminished clearance of the medicine. Patients with moderate to severe impairment of renal function should not receive ketorolac trometamol (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Mild Renal Impairment, for dosage reduction in patients with mild renal impairment, i.e. serum creatinine < 180 micromol/L). Ketorolac trometamol should be used with caution in patients with a history of kidney disease. Renal function should be monitored in patients who have had more than a single intramuscular dose of ketorolac, particularly in elderly patients.

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

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 effect 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 (see Section 4.3 CONTRAINDICATIONS), may lead to renal dysfunction which could be exacerbated when ketorolac trometamol is administered. Therefore, volume depletion should be corrected and close monitoring of serum urea, serum creatinine and urine output is recommended until the patient is normovolaemic. In patients on renal dialysis, ketorolac trometamol clearance is reduced to approximately half the normal rate and terminal half-life increases approximately threefold.

Use in the Elderly

Because ketorolac trometamol is cleared somewhat more slowly by the elderly (see Section 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics in Special Populations) who are also more sensitive to the fluid retaining, gastrointestinal toxicity and renal impairment effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) of this medicine, extra caution and the lowest effective dose should be used when treating the elderly with ketorolac trometamol (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

The safety and efficacy in children have not been established, therefore, ketorolac trometamol is not recommended for use in children under 16 years of age (see Section 4.3 CONTRAINDICATIONS).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Protein Binding

Ketorolac trometamol is highly bound to human plasma protein (mean 99.2%) and binding is independent of concentration. The in vitro binding of warfarin to plasma proteins is only slightly reduced by ketorolac trometamol (99.5% control versus 99.3% binding with ketorolac trometamol concentrations of 5 to 10 microgram/mL). Ketorolac trometamol does not alter digoxin protein binding.

In vitro studies indicated that at therapeutic concentrations of salicylate (300 microgram/mL), the binding of ketorolac trometamol was reduced from approximately 99.2% to 97.5%. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, paracetamol, phenytoin, tolbutamide and piroxicam did not alter ketorolac trometamol protein binding. Because ketorolac trometamol is a highly potent drug and present in low concentrations in plasma, it would not be expected to displace other protein bound drugs significantly.

Enzyme Induction/Inhibition

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

Warfarin

The concurrent use of NSAIDs and warfarin has been associated with severe and sometimes fatal haemorrhage. The exact mechanism of the interaction between NSAIDs and warfarin is unknown but may involve enhanced bleeding from NSAID induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Ketorolac trometamol should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of drugs should be closely monitored.

Anticoagulant Therapy and Other Drugs Affecting Haemostasis

NSAIDs may enhance the effects of anticoagulants, such as warfarin, low molecular weight heparin and dextrans (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Haematological Effects). Unlike the prolonged effects from aspirin, platelet function returns to normal within 24 to 48 hours after ketorolac is discontinued.

Aspirin and Other Nonsteroidal Anti-inflammatory Drugs

In patients concurrently receiving aspirin or other NSAIDs, the risk of inducing serious NSAID related adverse effects may be increased (see Section 4.3 CONTRAINDICATIONS).

Pentoxifylline

When ketorolac trometamol is administered concurrently with pentoxifylline, there is an increased tendency to bleeding (see Section 4.3 CONTRAINDICATIONS).

Methotrexate

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

Angiotensin Converting Enzyme (ACE) Inhibitors

As with other NSAIDs, ketorolac may increase the risk of renal impairment associated with the use of ACE inhibitors, particularly in patients who are actually or effectively volume depleted.

Combination Use of ACE Inhibitors or Angiotensin Receptor Antagonists, Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly during initiation of the combination. The combination of drugs from these three classes should be used with caution, particularly in elderly patients or those with pre-existing renal impairment.

Diuretics

Ketorolac trometamol reduces the diuretic response to furosemide in normovolaemic healthy subjects by approximately 20%.

Nephrotoxic Agents

The use of drugs with nephrotoxic activity (e.g. aminoglycoside antibiotics) should be avoided when using ketorolac trometamol.

Selective Serotonin Reuptake Inhibitors (SSRIs)

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

Probenecid

Concomitant administration of oral ketorolac trometamol and probenecid resulted in decreased clearance of ketorolac trometamol and significant increases in ketorolac trometamol plasma levels (total area under the curve (AUC) increased approximately threefold from 5.4 to 17.8 microgram.hour/mL). Terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore, the concomitant use of ketorolac trometamol and probenecid is contraindicated.

Lithium

Inhibition of renal lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of ketorolac trometamol on plasma lithium has not been studied, but cases of increased plasma levels during ketorolac trometamol therapy have been reported.

Antiepileptic Drugs

Sporadic cases of seizures have been reported during concomitant use of ketorolac trometamol and antiepileptic drugs (phenytoin, carbamazepine).

Psychoactive Drugs

Hallucinations have been reported when ketorolac trometamol was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Ketorolac trometamol may impair fertility and is not recommended in women attempting to conceive.

Use in Pregnancy

Pregnancy category: C

Ketorolac trometamol is not recommended for use during pregnancy, labour and delivery (see Section 4.3 CONTRAINDICATIONS).

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause premature closure of the fetal ductus arteriosus (see Premature Closure of Fetal Ductus Arteriosus), fetal renal impairment leading to oligohydramnios and neonatal renal impairment (see Oligohydramnios and Neonatal Renal Impairment), inhibition of platelet aggregation, and delay labour and birth.

Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Reproduction studies with ketorolac trometamol have been performed in rabbits and rats at oral doses of 3.6 and 10 mg/kg/day, respectively. The results from these studies did not reveal any significant evidence of harm to the fetus. However, studies in rabbits have shown a small increase in the incidence of major vessel anomalies.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

Premature Closure of Fetal Ductus Arteriosus

NSAIDs may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at about 30 weeks of gestation (third trimester) and later. NSAIDs increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios and Neonatal Renal Impairment

Use of NSAIDs from about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit NSAID use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue NSAID treatment if oligohydramnios occurs and follow up according to clinical practice.

Use in Lactation

Ketorolac trometamol is not recommended for treatment of breastfeeding mothers (see Section 4.3 CONTRAINDICATIONS).

After a single oral administration of ketorolac trometamol 10 mg to humans, the maximum milk concentration observed was 7.3 nanogram/mL and the maximum milk to plasma ratio was 0.037. After one day of dosing (four doses/day (qid)), the maximum milk concentration was 7.9 nanogram/mL and the maximum milk to plasma ratio was 0.025.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of ketorolac trometamol. If patients experience these or other similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Doctors using ketorolac trometamol injection should be alert for the usual complications of nonsteroidal anti-inflammatory treatment.

The adverse effects listed below were reported to be probably related to ketorolac trometamol in clinical trials in which patients received up to 20 doses, in five days, of postoperatively administered ketorolac trometamol 30 mg IM and in clinical trials in which patients received up to eight doses in two days, of postoperatively administered ketorolac trometamol 30 mg intravenously.

Incidence Between 3% and 9%

Gastrointestinal disorders: nausea, dyspepsia, gastrointestinal pain.

Nervous system disorders: drowsiness.

Incidence Between 1% and 3%

Gastrointestinal disorders: diarrhoea.

General disorders and administration site conditions: oedema, injection site pain was reported by 2% of patients in multidose studies (compared with 5% for the morphine control group).

Nervous system disorders: dizziness, headache.

Skin and subcutaneous tissue disorders: sweating.

Incidence 1% or Less

Ear disorders: vertigo.

Eye disorders: abnormal vision.

Gastrointestinal disorders: constipation, flatulence, gastrointestinal fullness, liver function abnormalities, melaena, peptic ulcer, rectal bleeding, stomatitis, vomiting.

General disorders and administration site conditions: asthenia, excessive thirst.

Musculoskeletal and connective tissue disorders: myalgia.

Nervous system disorders: dry mouth, paraesthesia, stimulation, abnormal taste.

Psychiatric disorders: nervousness, abnormal thinking, depression, euphoria, insomnia, inability to concentrate.

Renal and urinary disorders: increased urinary frequency, oliguria.

Respiratory, thoracic and mediastinal disorders: dyspnoea, asthma.

Skin and subcutaneous tissue disorders: pruritus, urticaria, purpura.

Vascular disorders: vasodilation, pallor.

Post-marketing Adverse Effects

The following international post-marketing adverse effects, although rare, have been reported spontaneously for patients who have received ketorolac trometamol.

Blood and lymphatic system disorders: thrombocytopenia, epistaxis, haematoma, angioedema.

Cardiac disorders: bradycardia, palpitations, cardiac failure.

Ear disorders: hearing loss, tinnitus, vertigo.

Eye disorders: abnormal vision.

Gastrointestinal disorders: gastrointestinal haemorrhage, peptic ulceration, gastrointestinal perforation, nausea, vomiting, diarrhoea, flatulence, eructation, constipation, dyspepsia, abdominal pain/ discomfort, melaena, haematemesis, stomatitis, ulcerative stomatitis, oesophagitis, rectal bleeding, pancreatitis, dry mouth, fullness, exacerbation of colitis and Crohn's disease, gastritis.

General disorders and administration site conditions: weight gain, injection site reactions, pallor, fever, asthenia, oedema, excessive thirst, chest pain.

Hepatobiliary disorders: hepatitis, cholestatic jaundice, liver failure.

Immune system disorders: anaphylaxis, anaphylactoid reactions, hypersensitivity reactions such as flushing, rash, hypotension, bronchospasm and laryngeal oedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Anaphylactic Reactions).

Infection: infection, aseptic meningitis.

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

Metabolic and nutrition disorders: hyponatraemia, hyperkalaemia, anorexia.

Musculoskeletal and connective tissue disorders: myalgia.

Nervous system disorders: headache, dizziness, paraesthesia, convulsions, extrapyramidal symptoms, hyperkinesia, taste abnormality, dry mouth, drowsiness.

Psychiatric disorders: abnormal dreams, hallucinations, anxiety, psychotic reactions, abnormal thinking, depression, insomnia, nervousness, euphoria, impaired concentration ability.

Renal and urinary disorders: acute renal failure, urinary retention, increased urinary frequency, interstitial nephritis, nephritic syndrome, haemolytic uraemic syndrome, oliguria, flank pain with or without haematuria and/or azotaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Renal Impairment)

Pregnancy, puerperium and perinatal conditions: oligohydramnios, neonatal renal impairment

Reproductive system and breast disorders: female infertility.

Respiratory, thoracic and mediastinal disorders: asthma, dyspnoea, pulmonary oedema.

Skin and subcutaneous tissue disorders: rash, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), maculopapular rash, Lyell's syndrome, pruritus, urticaria, purpura, sweating.

Vascular disorders: hypotension, hypertension, flushing, pallor, postoperative wound haemorrhage (rarely requiring blood transfusion).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Single overdoses of ketorolac trometamol 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. 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 NSAID overdose. There are no specific antidotes. Dialysis does not significantly clear ketorolac from the blood stream.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Ketorolac trometamol inhibits the synthesis of prostaglandins and is considered to be a peripherally acting analgesic. It does not have known effects on opiate receptors. No evidence of respiratory depression has been observed after administration of ketorolac trometamol in controlled clinical trials. Ketorolac trometamol possesses no sedative or anxiolytic properties.

Clinical Trials

Controlled clinical trials studying acute severe pain following major surgical procedures, e.g. cholecystectomy, gastric bypass, abdominal hysterectomy, open reduction and fixation of fractures, lumbar laminectomy and extraction of multiple impacted third molar teeth, have established the efficacy of ketorolac trometamol relative to other analgesics.

Given postoperatively, ketorolac trometamol 30 mg intramuscularly has an onset of action and peak analgesic efficacy comparable to intramuscular morphine 12 mg or pethidine 100 mg, and is more effective than intramuscular morphine 6 mg or pethidine 50 mg.

Intramuscular ketorolac trometamol 30 mg has a longer duration of action than intramuscular morphine 12 mg or pethidine 100 mg. Intramuscular ketorolac trometamol 10 mg gives efficacy equal to or greater than intramuscular morphine 6 mg or pethidine 50 mg.

Drug abuse and physical dependence.

Ketorolac trometamol is not a narcotic agonist or antagonist. Subjects did not show any subjective symptoms or objective signs of drug withdrawal upon abrupt discontinuation of intramuscular dosing. Ketorolac trometamol did not exhibit activity in classical animal studies that are reasonable predictors of opiate analgesic action (hotplate and tail withdrawal test). Ketorolac trometamol does not bind to opiate receptors in vitro. These studies demonstrate that ketorolac trometamol does not have central opiate-like activity.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of ketorolac in humans following single or multiple intramuscular doses are linear.

Absorption

The intramuscular form of ketorolac is rapidly and completely absorbed (100% bioavailable). Steady-state plasma levels are achieved after dosing every six hours for one day. A mean peak plasma concentration of 2.2 microgram/mL occurs an average of 50 minutes after a single 30 mg dose.

Binding and Distribution

More than 99% of ketorolac trometamol in plasma is protein bound. Even at high plasma concentrations (10 microgram/mL) only approximately 5% of albumin binding sites will be occupied. Thus the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin however, will result in increased free drug concentrations. Plasma protein binding is independent of concentration. As ketorolac trometamol is a highly potent medicine and present in low concentrations in plasma, it would not be expected to displace other protein bound medicines significantly. Nearly all the medicine related material circulating in plasma is ketorolac trometamol (96%) or the pharmacologically inactive p-hydroxyketorolac. The mean apparent volume (Vbeta) of ketorolac trometamol following complete distribution was approximately 13 L (this parameter was determined from single dose data). Ketorolac trometamol poorly penetrates the blood brain barrier (levels in the cerebrospinal fluid were found to be 0.002 times or less than those in plasma). Ketorolac crosses the placenta mean umbilical/maternal vein concentration ratio for ketorolac trometamol was 0.116 and this ratio increased as the time from injection to sampling increased).

Ketorolac trometamol has been detected in human milk at low concentrations (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy and Use in Lactation).

Metabolism

Ketorolac trometamol is largely metabolised in the liver. The major metabolic path of ketorolac in humans is glucuronic acid conjugation. p-Hydroxylation is an additional minor pathway.

Excretion

The primary route of excretion of ketorolac and its metabolites (conjugates and a para-hydroxy metabolite) is in the urine (mean 91.4%) and the remainder (mean 6.1%) is excreted in the faeces. The terminal plasma half-life of ketorolac is approximately in the range of five to six hours. No changes in clearance occur with chronic dosing.

Pharmacokinetics in special populations

Use in the elderly.

The mean terminal plasma half-life of ketorolac trometamol increased from five to seven hours in the elderly (aged 65 to 78 years) compared with young healthy volunteers (based on single dose data). There was little difference in the C_{max} for the two groups.

Impaired renal function.

The mean half-life of ketorolac trometamol in patients with renal impairment is between 6 and 19 hours and is dependent on the extent of the impairment (based on single dose data). There is poor correlation between creatinine clearance and total ketorolac trometamol clearance in the elderly and populations with renal impairment ($r = 0.5$). In patients with renal disease, the area under the curve (AUC) increased by approximately 100% compared with healthy volunteers. The volume of distribution increases by up to 100%. The increase in volume of distribution of ketorolac trometamol implies an increase in unbound fraction. The AUC ratio of the ketorolac trometamol enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects.

Impaired hepatic function.

Patients with impaired hepatic function do not have any clinically important changes in ketorolac trometamol pharmacokinetics, although there is a statistically significant prolongation of T_{max} and terminal phase half-life compared to young healthy volunteers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are ethanol, sodium chloride, water for injections; sodium hydroxide or hydrochloric acid to adjust pH.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Each 1 mL injection is packed in a Type 1 clear glass prefilled syringes which contains 30 mg of ketorolac trometamol.

Pack sizes: Each carton contains 5 prefilled syringes.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 144524 – KETORAL ketorolac trometamol 30mg/1mL injection syringe

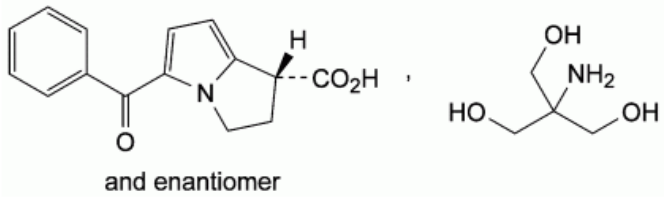
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Ketorolac trometamol is a member of the pyrrolo-pyrrole group of NSAIDs and is structurally and pharmacologically related to tolmetin and indometacin. However, unlike these pyrrole acetic acid derivatives, ketorolac is a cyclic propionic derivative. It is commercially available as the racemate; the (-)-(S)- isomer of ketorolac is the active isomer.



Ketorolac trometamol is a white to off white crystalline substance which discolours on exposure to light. It is soluble in water.

Chemical name: (±)-2-benzoyl-1-azabicyclo [3,3,0]octa-2,4-diene-6-carboxylic acid, 2-amino-2-hydroxymethylpropane-1,3-diol salt

Molecular formula: $C_{15}H_{13}NO_3$

Molecular weight: 255.27

CAS Number

74103-07-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

11/02/2009

10 DATE OF REVISION

01/07/2024

Summary Table of Changes

Section Changed	Summary of New Information
2	Update S1 declaration
All	Minor editorial changes

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