SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ketorolac Trometamol Rompharm 30 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution for injection contains 30 mg of ketorolac trometamol.

Excipient with known effect:
Each millilitre of solution contains 100 mg of ethanol (96%) and less than 1 mmol (23 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, slightly yellow solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ketorolac Trometamol Rompharm 30 mg/ml, solution for injection is indicated for the short-term management of moderate to severe acute post-operative pain. The maximum duration of treatment is two days.

4.2. Posology and method of administration

The time to onset of analgesic effect following both intramuscular and the intravenous administration is similar and is approximately 30 minutes, the maximum analgesia occurring within 1 - 2 hours.

The median duration of the analgesia is generally four to six hours.

Dosage should be adjusted individually, according to the severity of pain and the patient's response.

The administration of continuous multiple daily doses of ketorolac intramuscularly or intravenously should not exceed 2 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 minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Posology

The product is not approved for use after heart surgeries.

Adults and adolescents over 16 years

The recommended initial dose is 10 mg of ketorolac trometamol, followed by 10 to 30 mg every 4 to 6 hours, as required.
The minimum effective dose is recommended.

The recommended maximum daily dose is 90 mg of ketorolac trometamol (3 ampoules of Ketorolac Trometamol Rompharm) for adults and 60 mg ketorolac trometamol (2 ampoules of Ketorolac Trometamol Rompharm) for elderly patients and patients less than 50 kg.

The maximum duration of treatment should not exceed 2 days.

Patients receiving ketorolac trometamol on intravenous or intramuscular route, and who are converted to oral ketorolac, should receive a total combined daily dose of both pharmaceutical form not exceeding 90 mg ketorolac trometamol (3 ampoules of Ketorolac Trometamol Rompharm) for adults and 60 mg ketorolac trometamol (2 ampoules of Ketorolac Trometamol Rompharm) for the elderly, and patients less than 50kg.

Also, the oral component should not exceed 40 mg ketorolac trometamol on the day when the change of formulation is made from intramuscular route or intravenous to the oral route of administration. Patients should be converted to oral treatment as soon as possible.

The dosage should be reduced in patients under 50 kg.

Opioid analgesics (e.g., morphine, pethidine) may be administered concomitantly if they are necessary for an optimal analgesic effect or for their anxiolytic and/or sedative effects.

Ketorolac Trometamol Rompharm 30 mg/ml is not an opioid analgesic.
Ketorolac trometamol does not interfere with the opioid binding and does not exacerbate opioid-related respiratory depression or sedation.
When opioids are used in association with Ketorolac Trometamol Rompharm 30 mg/ml administered intramuscularly or intravenously, the daily dose of opioids should be lower than the usual one. However, opioids side-effects should still be considered, especially in the day of the surgical intervention.

Elderly (over 65 years)
The elderly have an increased risk of severe adverse reactions. If the administration of the anti-inflammatory drugs is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patients should be monitored regularly for gastrointestinal bleeding during treatment with non-steroidal anti-inflammatory drugs. The maximum daily dose should not exceed 60 mg of ketorolac trometamol (2 ampoules of Ketorolac Trometamol Rompharm). The doses should be reduced in the patients less than 50 kg.

Patients with renal impairment
Ketorolac Trometamol Rompharm 30 mg/ml is contraindicated in patients with moderate to severe renal impairment (See section 4.3); reduce dosage in lesser impairment (not exceeding 45mg/day IV or IM).

Children and adolescents
The safety and the efficacy of the administration in children and adolescents have not been established. For this reason, Ketorolac Trometamol Rompharm 30 mg/ml is contraindicated in children less than 16 years of age.

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

Method of administration

Ketorolac Trometamol Rompharm is for administration by intramuscular or bolus intravenous injection.
Bolus intravenous doses should be given over at least 15 seconds. Ketorolac Trometamol Rompharm 30 mg/ml should not be administered epidural or intrathecal. The treatment should be initiated and administered by qualified personnel.

4.3 Contraindications

Hypersensitivity to ketorolac or to other non-steroidal anti-inflammatory drugs (NSAIDs) and in patients in whom aspirin and other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients), or to any of the excipients listed in section 6.1.

Ketorolac is contraindicated in patients with a history of bronchial asthma.
Ketorolac is contraindicated in patients with complete or partial syndrome of nasal polyps, angioedema or bronchospasm.

As with other NSAIDs, ketorolac is contraindicated in patients with severe heart failure, hepatic failure and renal failure (see section 4.4).

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

Ketorolac is contraindicated in the patients with active peptic ulcer, with a history of gastrointestinal bleedings, ulceration or perforation, in patients with gastrointestinal bleedings or active perforations related to previous NSAIDs therapy, in patients with a history of peptic ulcer or gastrointestinal haemorrhage, and in patients with active gastrointestinal haemorrhage (two or more episodes of ulceration or bleeding).

Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients who 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.

Ketorolac is contraindicated in the patients who receive treatment with oral anticoagulants, including warfarin, and low dose heparin (2500 - 5000 IU twelve hourly).

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

The combination of ketorolac with oxpentifylline (pentoxifylline), lithium salts, probenecid is contraindicated.

Ketorolac is contraindicated in children and adolescents less than 16 years of age.

Ketorolac is contraindicated during pregnancy, labour, delivery or lactation (see section 4.6).

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

Ketorolac Trometamol Rompharm 30 mg/ml solution for injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.

4.4 Special warnings and precautions for use

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 of time (see also sections 4.1, 4.2 and 4.3).

Physicians should be aware that in some patients pain relief may not occur until upwards of 30 minutes after intravenous or intramuscular administration.

The use of ketorolac with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

The elderly patients have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleedings or perforations which may be fatal (see section 4.2 and the cardiovascular and the gastrointestinal risks listed below). 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.

Gastrointestinal bleeding, ulceration and perforation:
Gastrointestinal 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 gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, including ketorolac administered intravenously, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly patients. These patients should commence on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see section 4.5).

Patients with a history of gastrointestinal toxicity, particularly if elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

The concomitant use of anticoagulants, such as warfarin, is contraindicated (see section 4.3).

NSAIDs should be given with caution in patients with a history of gastrointestinal diseases (ulcerative colitis, Crohn's disease) as these may be exacerbated (see section 4.8). When gastrointestinal bleeding or ulcerations occur in patients receiving ketorolac trometamol intravenously, the treatment should be withdrawn.

As with other NSAIDs, the incidence and severity of the gastrointestinal complications may increase with increasing dose and duration of treatment with ketorolac trometamol administered intravenously. The risk of clinically serious gastrointestinal bleeding is dose-dependent. This is particularly true in elderly patients who receive an average daily dose of ketorolac trometamol administered intravenously greater than 60 mg/day. A history of peptic ulcer disease increases the possibility of developing serious gastrointestinal complications during treatment with ketorolac trometamol.

Haematological effects:

The use of ketorolac trometamol in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Although studies do not indicate a significant interaction between ketorolac trometamol and warfarin or heparin, the concurrent use of ketorolac trometamol and therapy that affects haemostasis, including therapeutic doses of anticoagulation therapy, i.e., warfarin, prophylactic low-dose heparin (2500-5000 units 12-hourly) and dextran, may be associated with an increased risk of bleeding. The administration of ketorolac trometamol to such patients should be done extremely cautiously, and these patients should be closely monitored.
In post-marketing experience, postoperative haematomas and other signs of wound bleeding have been reported in association with the peri-operative use of ketorolac trometamol, solution for injection. Physician should be aware of the potential risk of bleeding when haemostasis is critical in cases such as, but not limited to, resection of the prostate, tonsillectomy, cosmetic surgery.

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions at the beginning of therapy. Treatment with ketorolac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity**.**

Sodium/fluid retention in cardiovascular diseases and peripheral oedema:
Caution is recommended 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 and 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 treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

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.

Anaphylactic (anaphylactoid) reactions:
Anaphylactic (anaphylactoid) reactions (including, but not limited to, anaphylaxis, bronchospasm, vasomotor reactions, skin rashes, hypotension, laryngeal oedema and angioedema) may occur in patients with or without a history of hypersensitivity to aspirin, other NSAIDs or ketorolac. These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, ketorolac should 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 intravenous ketorolac, 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 infertility, withdrawal of ketorolac 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 probenecid is administered concurrently since alterations in the pharmacokinetics of ketorolac have been reported with this combination.
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 Trometamol Rompharm 30 mg/ml solution for injection is contraindicated in children and adolescents under 16 years of age (see section 4.3).

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

Excipients:
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., that is to say essentially “sodium-free”.

This medicinal product contains alcohol (ethanol) 100 mg in each ml. The amount in one ml of this medicine is equivalent to less than 2.5 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

It is contraindicated the association of ketorolac trometamol with other NSAIDs, oxpentifylline (pentoxifylline), probenecid and lithium salts (see section 4.3).

It is also contraindicated the association of ketorolac trometamol with anti-platelet agents, oral anticoagulants and heparin (see section 4.3).

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). 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.

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.

In patients currently receiving acetylsalicylic acid or other NSAIDs the risk of inducing serious NSAID-related adverse events may be increased.

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Probenecid should not be co-administered with ketorolac due to increased ketorolac plasma concentrations and half-life.

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

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.

Ketorolac trometamol does not alter the digoxin protein binding. *In vitro* studies indicate that, at therapeutic concentrations of salicylate (300 μg/ml), the binding of ketorolac was reduced from approximately 99.2 to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma concentrations. The therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, paracetamol, phenytoin and tolbutamide do not affect the protein binding of ketorolac trometamol.

Ketorolac solution for injection reduces the diuretic response to furosemide in normovolaemic healthy subjects by approximately 20%, therefore, particular care should be taken in patients with cardiac decompensation.

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 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 hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Caution is required for the concomitant administration with quinolones because of the risk of the occurrence of convulsions.

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

4.6 Fertility, pregnancy and lactation

Fertility

The use of ketorolac, 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 infertility, withdrawal of ketorolac should be considered. See section 4.4 regarding female fertility.

Pregnancy
In humans, no clinical trials have been performed to detect teratogenic effects.
As with other NSAIDs, during the third trimester of pregnancy, ketorolac trometamol favours the premature closure of the ductus arteriosus. Administered in the perinatal period, it can cause heavy bleeding.

Ketorolac is contraindicated during pregnancy, labour, delivery or lactation (see section 4.3).

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-hydramnios;

Oligohydramnios/Neonatal Renal Impairment:
Use of NSAIDs, including Ketorolac, at 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 postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

The mother and the neonate, at the end of the pregnancy, to:
- Possible prolongation of the 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 up to 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.

Breast-feeding mothers
Ketorolac has been detected in human milk at low concentrations. The administration of ketorolac is contraindicated during the breast-feeding period.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Blood and lymphatic disorders:
Thrombocytopenia

Immune system disorders:
Anaphylaxis, anaphylactoid reactions like anaphylaxis, may have a fatal outcome, hypersensitivity reactions such as bronchospasm, rash, hypotension, laryngeal oedema.

Metabolic and nutrition disorders:
Anorexia, hyperkalaemia, hyponatraemia

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

Nervous system disorders:
Headache, dizziness, convulsions, paraesthesia, hyperkinesia, taste abnormalities.

Eye disorders:
Vision disorders

Ear and labyrinth 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 and/or azotemia). As with other drugs that inhibit prostaglandin synthesis, signs of renal impairment, such as (but not limited to) elevations of serum creatinine and potassium can occur even after a single dose of ketorolac trometamol.

Cardiac disorders:
Palpitations, bradycardia, cardiac failure.

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

Clinical trial and epidemiological data suggest that the use of the 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 been 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:
Bronchial asthma, dyspnoea, pulmonary oedema.

Hepatobiliary disorders:
Hepatitis, cholestatic jaundice, liver failure.

Skin and subcutaneous tissue disorders.
Exfoliative dermatitis, maculopapular rash, pruritus, purpura, angioedema, sweating, bullous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (very rarely).

Musculoskeletal and connective tissue disorders.
Myalgia

General disorders and administration site conditions:
Excessive thirst, asthenia, oedema, injection site reactions, fever, chest pain.

Diagnostic investigations.
Bleeding time prolonged, serum urea increased, creatinine increased, abnormal liver function tests.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important.
It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/.

4.9 Overdose

Symptoms and signs
Single overdoses of ketorolac trometamol have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcer and/or erosive gastritis and renal dysfunction, which have resolved after discontinuation of drug administration.
Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may also occur after the ingestion of NSAIDs, but only in rare cases.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment:
Symptomatic treatment and support of vital functions should be instituted. There is no specific antidote. Dialysis does not significantly clear ketorolac from the blood stream.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinflammatory and antirheumatic products, non-steroids; acetic acid derivatives and related substances, ATC code: M01AB15

Ketorolac trometamol is not an opioid analgesic. Ketorolac inhibits synthesis of prostaglandins and may be considered a peripherally-acting analgesic since it does not have known effect on opioid receptors. It is a non-steroidal drug with a weak anti-inflammatory and antipyretic activity.

5.2 Pharmacokinetic properties

Following intramuscular administration, ketorolac trometamol is rapidly and completely absorbed, a mean peak plasma concentration of 2.2mcg/ml occurring an average of 50 minutes after a single 30 mg dose of ketorolac trometamol.
More than 99% of the ketorolac trometamol in plasma is protein-bound.
The pharmacokinetics of ketorolac trometamol administered intramuscular following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every 6 hours, for one day. The terminal plasma half-life is 5.3 hours in young adults and 7 hours in elderly (mean age 72 years). No changes in clearance occurred with chronic dosing.

Hemodynamic of patient is not altered by parenteral administration of ketorolac trometamol. The primary route of excretion of ketorolac trometamol and its metabolites (conjugates and para-hydroxy metabolites) is renal (approximately 91.4%, mean), while the rest is eliminated in the faeces (6.4%, mean).

5.3 Preclinical safety data

No teratogenic effects were observed in rabbits receiving oral doses of up to 3.6 mg/kg per day.
No carcinogenic effects were observed in long-term studies in mice (2 mg/kg per day, equivalent to the maximum parenteral dose recommended in humans).
There were no evidence of mutagenic effects in Ames test and other mutagenicity tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%
Sodium chloride
Disodium edetate
Sodium hydroxide solution 1M
Sodium hydroxide or hydrochloric acid (1M solutions for pH adjustment)
Water for injections

6.2 Incompatibilities

It is not recommended the mixing in a small volume (e.g., in a syringe) with morphine sulfate, pethidine hydrochloride, promethazine hydrochloride, hydroxyzine hydrochloride, as precipitation of ketorolac trometamol will occur.
It is compatible with normal saline, dextrose 5%, Ringer's solution, lactated Ringer's solution.
The compatibility of ketorolac with other drugs is not known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C with the diluents detailed in section 6.2.
From a microbiological point of view, unless the method of opening and dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.
Store in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Box with 5 ampoules of amber, type 1 glass, with break-ring; each ampoule contains 1 ml solution for injection.
Box with 10 ampoules of amber, type 1 glass, with break-ring; each ampoule contains 1 ml solution for injection.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

S.C. Rompharm Company S.R.L.
Eroilor Street, no. 1A, Otopeni, Ilfov County, 075100, Romania

8. MARKETING AUTHORIZATION HOLDER

A.L. Medi Market Ltd, 3 Hakatif Street, Emek Hefer Industrial Park, 3877701, Israel

9. MARKETING AUTHORIZATION NUMBER(S)

165-53-35519-00

10. DATE OF REVISION OF THE TEXT

Revised in June 2021 according to MoHs guidelines