SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
KETAVEL 50 mg/2 ml Solution for IM/IV Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule contains in 1 ml:
Active substance:
36.9 mg dexketoprofen trometamol equivalent to 25 mg dexketoprofen.

In 2 ml (total volume) 73.8 mg dexketoprofen trometamol equivalent to 50 mg dexketoprofen.

Excipients:
Each 2 ml ampoule contains

Ethanol (96%)	200 mg
Sodium chloride	8 mg
Sodium hydroxide	q.s. (for pH adjustment)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection
Almost colorless and clear solution
pH (7.7-9)
Osmolarity (270-410 mOsmol/kg)

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is indicated for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, as well as acute gouty arthritis, acute musculoskeletal pain (e.g. low back pain), post-operative pain, dysmenorrhea and renal colic.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
Adults
The recommended dose is 50 mg every 8–12 hours. It can be administered at 6 hour intervals, provided that the maximum daily dose of 150 mg is not exceeded.

KETAVEL is intended for short term use and the treatment must be limited to the acute symptomatic period (maximum 2 days). Patients should be switched to an oral analgesic treatment when possible.

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

In case of moderate to severe postoperative pain, KETAVEL can be used in combination with opioid analgesics, if indicated, at the same recommended doses in adults (see section 5.1).

Method of administration:
KETAVEL can be administered either by intramuscular or by intravenous route.

IM administration:
The content of 1 KETAVEL (2 ml) should be administered by slow injection deep into the muscle.

IV administration:
IV infusion: The diluted solution, prepared as described in section 6.6, should be administered as a slow intravenous infusion, for 10 to 30 min. The solution must be always protected from sunlight.

IV bolus: If necessary, the content of 1 KETAVEL (2 ml) may be given by slow IV bolus over 15 seconds.

Instructions on handling the medicine:
When KETAVEL is administered IM or as IV bolus, the solution should be injected immediately after its removal from the colored ampoule (see sections 6.2 and 6.6).

When administered as IV infusion, the solution should be diluted aseptically and protected from sunlight (see sections 6.3 and 6.6). For instructions on dilution of the medicinal product before administration, see Section 6.6.

Additional information on special populations
Renal impairment:
The dosage should be reduced to 50 mg total daily dose in patients with mildly impaired renal function (creatinine clearance 60-89 ml/min) (see section 4.4). KETAVEL should not be used in patients with moderate to severe renal failure (creatinine clearance ≤59 ml/min) (see section 4.3).

Hepatic impairment:
The dosage should be reduced to 50 mg total daily dose in patients with mild and moderate (Child-Pugh score 5-9) hepatic impairment and hepatic function should be closely monitored during the use of drug (see section 4.4). KETAVEL should not be used in patients with severe hepatic impairment (Child-Pugh score 10-15) (see section 4.3).

Pediatric population:
There are no studies conducted with KETAVEL in children and adolescents. Therefore, it should not be used in children and adolescents as its safety and effectiveness have not been proven.

Geriatric population:
Dose adjustment is usually not necessary in the elderly. Because of the physiological decline in renal function in elderly patients a lower dose (50 mg total daily dose) is recommended in case of mild renal function impairment (see section 4.4).

4.3 Contraindications
KETAVEL must not be administered in the following cases:
- In patients with sensitivity to dexketoprofen, to any other NSAID, or any of the excipients of this medicine listed in section 6.1
- It should not be used in patients with asthma, urticaria or allergic-type reactions (bronchospasm, acute rhinitis, or nasal polyps, urticaria or angioneurotic edema) as a result of taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4).
- In known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates

- In patients with active or suspected peptic ulcer/gastrointestinal bleeding or any history of gastrointestinal bleeding, ulceration or perforation
- In patients with history of chronical dyspepsia
- In patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- In patients with other active bleeding or bleeding disorders
- In patients with Crohn's disease or ulcerative colitis
- In patients with severe heart failure.
- In patients with moderate to severe kidney failure (creatinine clearance ≤59 ml/min).
- In patients with severe liver failure (Child-Pugh score 10-15).
- In patients with hemorrhagic diathesis and other coagulation disorders.
- In patients with severe dehydration (due to vomiting, diarrhea or insufficient fluid intake),
- During the third trimester of pregnancy and lactation period (see section 4.6).
- KETAVEL is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4).

KETAVEL is contraindicated for neuraxial (intrathecal or epidural) administration due to its ethanol content.

4.4 Special warnings and precautions for use

Cardiovascular risk:
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see Warnings).
- KETAVEL is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Warnings).

Gastrointestinal (GI) risk:
- NSAIDs cause serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and with or without any previous warning symptoms. Elderly patients are at greater risk for serious GI events (see Warnings).

The safe use in children and adolescents has not been established.
Administer with caution in patients with a history of allergic conditions.

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

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular risks below).

Gastrointestinal (GI) effects – the risk of ulceration, bleeding or perforation
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. When gastrointestinal bleeding or ulceration occurs in patients

receiving KETAVEL, the treatment should be discontinued.

The risk of gastrointestinal bleeding, ulcers or perforation increases as the dose of NSAID is increased, especially in patients with a history of ulcers with bleeding or perforation (see section 4.3) and in elderly individuals.

Only one in five patients, who develop a serious GI adverse event during treatment with NSAID, is symptomatic. Upper GI ulcers, major bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. The continuation of these trends during long-term treatment increases the likelihood of a serious GI event at any stage of the patient's treatment. However, even short-term therapy is not without risk.

Patients with a prior history of ulceration and/or gastrointestinal bleeding who use NSAID's have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that may increase the risk for GI bleeding in patients treated with NSAIDs include treatment with oral corticosteroids, treatment with anticoagulants, prolonged treatment with NSAIDs, smoking, use of alcohol, older age, and poor general health status.

To minimize the potential risk of an adverse GI event, patients should be treated for the shortest possible duration and with the lowest effective dose of NSAID. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and additional treatment if a serious GI adverse event is suspected. If the serious adverse event does not disappear, NSAID treatment should be stopped. In high-risk group patients, alternative therapies that do not include NSAIDs should be planned.

Elderly: The frequency of NSAID-induced adverse reactions, especially gastrointestinal bleeding and perforation, which can be fatal, is increased in the elderly (see section 4.2). These patients should start treatment at the lowest appropriate dose.

As with all NSAIDs, a history of esophagitis, gastritis and/or peptic ulcer should be investigated to ensure that they are completely healed before starting treatment with dexketoprofen trometamol. Patients with gastrointestinal symptoms or a history of gastrointestinal disease should be monitored for digestive disorders, especially gastrointestinal bleeding.

Combination therapy with prophylactic agents (e.g. misoprostol or proton pump inhibitors) should be considered in these patients, and in patients who need to take concomitant low-dose acetylsalicylic acid or other medicines that are likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when 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, warfarin-like anticoagulants, selective serotonin-reuptake inhibitors or acetylsalicylic acid-like anti-platelet agents (see section 4.5).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time via inhibition of prostaglandin synthesis. The concomitant use of dexketoprofen trometamol and prophylactic doses

of low molecular weight heparin in the postoperative period has been assessed in controlled clinical trials and no effect on coagulation parameters was observed. Nevertheless, patients receiving treatments that affect haemostasis, such as warfarin, other coumarins or heparins, should be carefully monitored if they have received dexketoprofen trometamol (see section 4.5).

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 edema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of 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). There are insufficient data to exclude such a risk for dexketoprofen trometamol.

Renal effects:
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Additionally, renal toxicity has also been seen in patients because renal prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory medicine may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin converting enzyme (ACE) inhibitors, and the elderly.

Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

As with all NSAIDs, dexketoprofen trometamol may increase plasma urea nitrogen and creatinine. As with other prostaglandin synthesis inhibitors, it may be associated with renal system side effects which may lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, and acute renal failure.

Advanced renal diseases:
KETAVEL is contraindicated in patients with moderate - severe renal impairment (creatinine clearance ≤59 ml/min).

Cardiovascular thrombotic incidents:
An increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal, has been observed in clinical trials of up to 3 years with many selective and non-selective COX-2 inhibitors. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known cardiovascular disease or at risk for cardiovascular disease may be at higher risk. To reduce the potential risk of adverse cardiovascular events in patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. The patient should be informed in advance about the symptoms and/or signs of serious cardiovascular events and what to do if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID do increase the risk of serious GI events.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see section 4.3 Contraindications).

KETAVEL is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4).

Consequently, patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with dexketoprofen trometamol after careful consideration. Similar consideration should be made before initiating long-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking).

It should be used with caution in patients with hepatic and/or renal dysfunction, as well as in people with a history of hypertension and/or heart failure. In such patients, the use of NSAIDs may result in worsening renal function, fluid retention, and edema. Caution should also be exercised in patients receiving diuretic therapy or who develop hypovolemia, as there is an increased risk of nephrotoxicity. It should be used with particular caution in patients with a history of cardiac disease, especially in patients with a history of heart failure, due to the increased risk of triggering heart failure.

Hypertension:
As with all other NSAIDs, dexketoprofen may cause hypertension or worsen pre-existing hypertension, and both of which may increase the risk of cardiovascular events. Patients treated with thiazide diuretics or loop diuretics may have a reduced response to diuretic therapy while taking NSAIDs. NSAIDs, including dexketoprofen, should be used with caution in patients with hypertension. Blood pressure (BP) should be closely monitored at the beginning of dexketoprofen therapy and throughout treatment.

Congestive heart failure and edema:
Fluid retention and edema have been observed in some patients taking NSAIDs, including dexketoprofen. Therefore, dexketoprofen should be used with caution in patients with heart failure and fluid retention.

Skin reactions
Very rarely, some fatal serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with the use of NSAIDs including dexketoprofen (see section 4.8). These serious events can occur without any warning. Patients should be informed in advance of the signs and symptoms of serious skin reactions and KETAVEL should be discontinued at the first sign of skin rash, mucosal lesions or any other signs of hypersensitivity.

Exceptionally, varicella can be a source of serious cutaneous and infectious soft tissue complications. To date, the contribution of NSAIDs to the worsening of these infections has not been ruled out. Therefore, it is recommended not to use KETAVEL in the case of varicella.

Anaphylactoid reactions:
As with other NSAIDs, anaphylactoid reactions, may occur with dexketoprofen in patients without

known prior exposure to the drug. KETAVEL should not be given to patients with the aspirin triad (Analgesic intolerance or acetylsalicylic acid intolerance (ASAI) in asthmatics is called the "Aspirin triad"). This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see Sections 4.3 and 4.4- Special warnings and precautions for use - Preexisting asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Pregnancy:
In third trimester pregnancy, as with other NSAID's, dexketoprofen should be avoided; because it may cause premature closure of the ductus arteriosus (the opening between the two large arteries [aorta and pulmonary artery] coming out of the heart, which is open in the womb and must close after birth). KETAVEL is contraindicated during 3rd trimester of pregnancy and lactation.

KETAVEL should be used with caution in patients with haematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease.

Like other NSAIDs, dexketoprofen may mask the symptoms of infectious diseases. Transient aggregation of soft tissue infections has been reported in isolated cases with the use of NSAIDs. Therefore, if symptoms of bacterial infection appear or worsen during treatment, the patient is advised to consult a physician immediately.

Each KETAVEL contains 200 mg ethanol, equivalent to 5 ml of beer or 2.08 ml of wine. It may be harmful to those with alcohol dependence. It should be taken into consideration in pregnant or lactating women, children and patients with high-risk groups such as liver disease or epilepsy.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially "sodium-free".

Precautions
General:
Dexketoprofen should not be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may cause the exacerbation of the disease. If corticosteroid therapy is to be discontinued in patients receiving long-term corticosteroid therapy, treatment should be reduced slowly and gradually.

The pharmacological activity of KETAVEL in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic effects:
Like all other NSAIDs, it may cause transient small increases in some liver parameters and significant increases in SGOT and SGPT. If relevant increases in such parameters occur, treatment should be discontinued.

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including dexketoprofen. These laboratory abnormalities may progress, remain unchanged, or resolve spontaneously with continued therapy. Severe elevations of ALT and AST activity (three times or more the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. Rare cases of jaundice and severe hepatic reactions, including fatal fulminant hepatitis,

hepatic necrosis, and hepatic failure, some with fatal outcomes, have also been reported.

Patients with symptoms suggestive of liver dysfunction or abnormal liver test results should be evaluated for the possibility of developing more serious hepatic reactions during treatment with dexketoprofen. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations (e.g. eosinophilia, skin rash, etc.) are observed, treatment with KETAVEL should be discontinued and appropriate investigations should be requested.

Hematologic effects:
Anemia is sometimes seen in patients receiving NSAIDs, including dexketoprofen. This may be due to fluid retention, occult or overt GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including dexketoprofen, should have their hemoglobin or hematocrit checked regularly if they exhibit any signs or symptoms of anemia.

NSAIDs have been shown to prolong bleeding time by inhibiting platelet aggregation in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients with pre-existing coagulation disorders or who are taking anticoagulants and who are likely to experience adverse effects due to changes in platelet function should be carefully monitored during the use of KETAVEL.

Preexisting asthma:
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, KETAVEL should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Laboratory tests:
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Complete blood count and biochemistry profiles should be checked periodically in patients receiving long-term NSAID therapy. If clinical signs and symptoms consistent with liver or renal disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests are abnormal or worsen, KETAVEL treatment
should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction
The following interactions apply to non-steroidal antiinflammatory drugs (NSAIDs) in general:

Inadvisable combinations:
- Other NSAIDs, including high dose silicates (≥ 3 g/day): Simultaneous use of several NSAIDs should be avoided, as they may increase the risk of gastrointestinal ulcers and bleeding through synergistic effects.
- Anticoagulants: NSAIDs may increase the effects of warfarin-like anti-coagulants due to the high binding of dexketoprofen to plasma proteins, inhibition of platelet function and gastroduodenal mucosal damage (see section 4.4). If the combination cannot be avoided, close clinical observation and laboratory values should be monitored.
- Heparins: Increased risk of hemorrhage (due to the inhibition of platelet function and damage to

the gastroduodenal mucosa). If the combination cannot be avoided, close clinical observation and monitoring of laboratory values should be carried out.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Lithium (described with several NSAIDs): NSAIDs increase blood lithium levels, which may reach toxic values (decreased renal excretion of lithium). This parameter therefore requires monitoring during the initiation, adjustment and withdrawal of treatment with dexketoprofen.
- Methotrexate, used at high doses of 15 mg/week or more: Increased hematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general.
- Hydantoines and sulphonamides: The toxic effects of these substances may be increased.

Combinations requiring precautions:
- Diuretics, ACE inhibitors, antibacterial aminoglycosides and angiotensin II receptor antagonists: Dexketoprofen may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e. g. dehydrated patients or elderly patients with compromised renal function), the coadministration of agents that inhibit cyclo-oxygenase and ACE inhibitors or angiotensin II receptor antagonists or antibacterial aminoglycosides may result in further deterioration of renal function, which is usually reversible. In case of combined prescription of dexketoprofen and a diuretic, it is essential to ensure that the patient is adequately hydrated and to monitor renal function at the start of the treatment (see section 4.4).
- Methotrexate, used at low doses, less than 15 mg/week: Increased hematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory agents in general. Blood counts should be monitored weekly during the first weeks of the combination. Monitoring should be increased in patients with mild renal dysfunction and in the elderly.
- Pentoxyfylline: There may be an increased risk of bleeding. Clinical monitoring should be increased and bleeding time should be checked more frequently.
- Zidovudine: Risk of increased red cell line toxicity via action on reticulocytes, with severe anemia occurring one week after the NSAID is started. Check complete blood count and reticulocyte count 1-2 weeks after starting treatment with the NSAIDs.
- Sulfonylureas: NSAIDs can increase the hypoglycemic effect of sulfonylureas by displacement from plasma protein binding sites.

Combinations needing to be taken into account:
- Beta-blockers: Treatment with a NSAID may decrease their antihypertensive effect via inhibition of prostaglandin synthesis.
- Cyclosporine and tacrolimus: Nephrotoxicity may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combination therapy, renal function has to be measured.
- Thrombolytics: Increased risk of bleeding.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
- Probenecid: Plasma concentrations of dexketoprofen may be increased; this interaction can be due to an inhibitory mechanism at the site of renal tubular secretion and of glucuronoconjugation and requires adjustment of the dose of dexketoprofen.
- Cardiac glycosides: NSAIDs may increase plasma glycoside concentrations.
- Mifepristone: Because of a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, NSAIDs should not be used for 8-12 days after mifepristone administration.
- Quinolone antibiotics: Animal data indicate that high doses of quinolones in combination with NSAIDs can increase the risk of developing convulsions.

Additional information on special populations
Pediatric population:
There are no studies on KETAVEL in children and adolescents. Therefore, its safety and effectiveness have not been proven.

4.6 Pregnancy and Lactation
General recommendation
Pregnancy category: C in the 1st and 2nd trimester; It is D in the 3rd trimester.

Women of child-bearing potential/Birth control (Contraception)
Women of child-bearing potential should use an appropriate contraceptive method.

Pregnancy
KETAVEL is contraindicated during third trimester of pregnancy (see section 4.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo-fetus development. Data from epidemiological studies have raise concern about an increased risk of miscarriage, cardiac malformations and teratogenic effects, defined as a congenital cleft opening of the abdominal wall, after the use of prostaglandin synthesis inhibitors 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.

Dexketoprofen trometamol should not be given during the first and second trimesters of pregnancy unless absolutely necessary. If dexketoprofen trometamol is used by patients planning pregnancy or in the first or second trimester of pregnancy, the treatment dose should be as low as possible and the duration of treatment should be as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to the following risks:
- Cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction that may progress to renal failure accompanied by oligohydramnios;

The mother and the neonate may face the following risks, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- Inhibition of uterine contractions resulting in delayed or prolonged labor.

Lactation
KETAVEL is contraindicated during lactation.

It is not known whether dexketoprofen is excreted in human milk.

Reproductive ability / Fertility
As with other NSAIDs, the use of dexketoprofen trometamol may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of dexketoprofen trometamol should be considered. Dexketoprofen should not be used during the first and second trimesters of pregnancy unless clearly necessary.

4.7 Effects on ability to drive and use machines

KETAVEL may have a mild or moderate influence on the ability to drive and use machines as dizziness and drowsiness may occur.

4.8 Undesirable effects

Adverse reactions reported to be potentially related to dexketoprofen trometamol in clinical trials with parenteral dexketoprofen and adverse reactions reported after dexketoprofen trometamol was authorized are shown in the table below and the reactions are organized by system organ class and ordered according to the frequency of occurrence.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders		Anemia		Neutropenia, thrombocytopenia
Immune system disorders			Laryngeal edema	Anaphylactic reaction, anaphylactic shock
Metabolism and nutrition disorders			Hyperglycemia, hypoglycemia, hypertriglyceridemia, anorexia	
Psychiatric disorders		Insomnia		
Nervous system disorders		Headache, dizziness, somnolence	Paresthesia, syncope	
Eye disorders		Blurred vision		
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders			Extrasystole, tachycardia	
Vascular disorders		Hypotension, facial redness	Hypertension, superficial thrombophlebitis	
Respiratory, thoracic and mediastinal disorders			Bradypnea	Bronchospasm, dyspnea
Gastrointestinal disorders	Nausea, vomiting	Abdominal pain, dyspepsia, diarrhea, constipation, hematemesis, dry mouth	Peptic ulceration, peptic ulcer hemorrhage or perforation (see section 4.4)	Pancreatitis
Hepatobiliary disorders			Hepatitis, jaundice	Hepatic damage
Skin and subcutaneous tissue disorders		Dermatitis, pruritus, skin rash, sweating increased	Urticaria, acne	Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, facial

				edema, photosensitivity reactions
Musculoskeletal and connective tissue disorders			Muscle stiffness, joint stiffness, muscle cramps, back pain	
Renal and urinary disorders			Acute renal failure, Polyuria, renal pain, ketonuria, proteinuira	Nephritis or nephrotic syndrome
Reproductive system and breast disorders			Menstrual disorders, prostatic disorders	
General disorders and administration site conditions	Injection site pain, injection site reactions including inflammation, bruising or hemorrhage	Pyrexia, muscle fatigue, pain, feeling cold	Stiffness, peripheral edema	
Investigations			Abnormalities in liver function tests	

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 Special Warnings and Special Precautions for Use) have been reported following administration. Less frequently, gastritis has been observed.

Edema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

As with other NSAIDs the following undesirable effects may appear: Aseptic meningitis, which might predominantly occur in patients with systemic lupus erythematosus or mixed connective tissue disease; and hematological reactions (purpura, aplastic and hemolytic anemia, rarely agranulocytosis and medullar hypoplasia).

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare) have been reported.

Clinical trial and epidemiological data suggest that use of 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) (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local regulations.

4.9 Overdose
The symptoms following overdose is not known. Similar medicinal products have produced gastrointestinal (vomiting, anorexia, abdominal pain) and neurological (somnolence, vertigo,

disorientation, headache) disorders.

In case of accidental or excessive intake or administration, immediately institute symptomatic therapy.

Dexketoprofen trometamol may be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives, anti-inflammatory and antirheumatic products, non-steroids
ATC code: M01AE17

Dexketoprofen trometamol, the tromethamine salt of S-(+)-2-(3-benzoylphenyl) propionic acid, is an analgesic, anti-inflammatory and antipyretic drug belonging to the non-steroidal anti-inflammatory drug (NSAID) group.

Mechanism of action
The mechanism of action of dexketoprofen trometamol is related to the inhibition of prostaglandin synthesis by inhibition of the cyclooxygenase pathway.

In particular, the conversion of arachidonic acid to the prostaglandins PGE_1, PGE_2, $PGF_{2\alpha}$ and PGD_2, as well as the cyclic endoperoxides PGG_2 and PGH_2, which produce PGI_2 prostacyclin and thromboxanes (TxA2 and TxB2), is inhibited. In addition, the inhibition of prostaglandin synthesis affects other inflammatory mediators such as kinin, causing an indirect effect in addition to the direct effect.

Pharmacodynamic effects
Dexketoprofen has been demonstrated to be an inhibitor for COX-1 and COX-2 activities in experimental animals and humans.

Clinical efficacy and safety
Clinical studies performed on several pain models have shown that dexketoprofen trometamol has an effective analgesic activity.

The analgesic efficacy of IM and IV dexketoprofen trometamol for relief of moderate to severe pain was investigated in several surgical pain models (orthopedic and gynecologic/ abdominal surgery) as well as in musculo-skeletal pain (acute low back pain model) and renal colic.

In the studies performed, the onset of analgesic effect was rapid, and within the first 45 minutes the peak analgesic effect occurred. Duration of analgesic effect after the administration of 50 mg of dexketoprofen is usually 8 hours.

Clinical studies in postoperative pain management have demonstrated that dexketoprofen trometamol when used in combination with opioids significantly reduced the need for opioid. In the postoperative pain studies where patients received morphine by a patient controlled analgesia device, patients treated with dexketoprofen required significantly less morphine (between 30–45% less) than patients in the placebo group.

5.2 Pharmacokinetic properties

General properties

Absorption:

After IM administration of dexketoprofen trometamol, the peak concentrations are reached at 20 minutes (range 10 to 45 min). For 25 to 50 mg single dose the area under the curve (AUC) has been proved to be dose proportional after both IM and IV administration.

In multiple-dose pharmacokinetic studies, it was observed that C_{max} and AUC after the last IM or IV administration were not different from that obtained following a single dose. This is indicating that no drug accumulation occurs.

Distribution:

As with other drugs with a high plasma protein binding (99%), its volume of distribution has a mean value below 0.25 L/kg. The distribution half-life is approximately 0.35 hours.

Biotransformation:

After administration of dexketoprofen trometamol only the S-(+) enantiomer is obtained in urine, demonstrating that the S-(+)enantiomer is not converted to the R-(-)enantiomer in humans.

Elimination:

The elimination half-life varies between 1-2.7 hours. The main elimination route for dexketoprofen is renal excretion following glucuronide conjugation.

Linearity/Nonlinearity:

Dexketoprofen trometamol shows linear pharmacokinetics with dose proportional increases in systemic exposure following intramuscular and intravenous administration.

Characteristics in patients

Elderly:

At single and repeated oral doses, the residence time of the drug in the body is significantly longer (up to 55%) in healthy elderly subjects (65 years and older) than in younger volunteers. However, there is no statistically significant difference in peak concentrations and time to peak concentrations. The mean elimination half-life was prolonged after single and repeated doses (up to 48%), and the total clearance was reduced.

5.3 Preclinical safety data

Preclinical data do not reveal any special hazards for humans other than those already stated in other sections of the Summary of Product Characteristics based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity and immunopharmacology. Chronic toxicity studies in mice and monkeys have shown a No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day. The main adverse effects observed at high doses were dose-dependent gastrointestinal erosions and ulcers.

As accepted for all pharmacological classes of NSAIDs, dexketoprofen trometamol may cause differences in embryo-fetal survival in animal models, both indirectly through gastrointestinal toxicity in pregnant women and directly through effects on fetal development.

In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss and embryo-fetal death. Additionally, an increased incidence of

various malformations, including cardiovascular malformations, has been reported in animals given prostaglandin synthesis inhibitors during the period of organogenesis. However, animal studies with dexketoprofen trometamol have not shown reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96 %)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

KETAVEL must not be mixed in a small volume (e.g. in a syringe) with solutions of dopamine, promethazine, pentazocine, pethidine or hydroxyzine, as this will result in a precipitation of the solution.

The diluted solutions for infusion obtained as stated in section 6.6 must not be mixed with promethazine or pentazocine.

This product must not be mixed with any medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C, protect from light.
Keep the ampoules in the original carton package.

When KETAVEL 50 mg/2 ml Solution for IM/IV Injection is diluted in a volume of 30 mL-100 mL with different diluents such as isotonic sodium chloride 0.9 %, dextrose 5% and Ringer lactate, it is stabile for 2 hours when stored in room conditions and at 2-8°C and protected from light.

The product should be used immediately after being diluted.

6.5 Nature and contents of container

Coloured Type I glass ampoules (6 ampoules) containing 2 ml of injectable solution.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

When administered by IV route, the contents of one ampoule (2 ml) should be diluted to a volume of between 30 and 100 ml with normal saline, glucose or Ringer's lactate solution. The solution should be diluted aseptically and protected from sunlight (see section 6.3). The diluted solution should be clear.

Solutions diluted in 100 ml of normal saline or glucose solution for infusion have been shown to be compatible with the following drugs for injection: dopamine, heparin, hydroxyzine, lidocaine, morphine, pethidine and theophylline.

When solutions diluted with KETAVEL were stored in plastic containers or administered via devices made of Ethyl Vinyl Acetate (EVA), Cellulose Propionate (CP), Low Density Polyethylene (LDPE) or Poly Vinyl Chloride (PVC), no interaction between the active substance and the storage environment was observed.

KETAVEL is for single use and any unused solution should be discarded. Prior to administration, the solution should be inspected visually to make sure it is clear and colorless: it should not be used if particulate matter is observed.

7. MARKETING AUTHORIZATION HOLDER

Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No: 1 34303 Küçükçekmece-İSTANBUL-TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-mail: deva@devaholding.com.tr

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Date of first authorization : 01.07.2014
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10. DATE OF REVISION OF THE TEXT