SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KETAVEL 50 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Active substance:

Dexketoprofen_____50 mg (equivalent to 73.8 mg dexketoprofen trometamol)

Excipients with known effect:

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, white film-coated tablet with a notch on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as for the treatment of acute gout arthritis, acute musculoskeletal pain, postoperative pain, and dysmenorrhea.

4.2. Posology and method of administration

Posology / Frequency of administration and duration

For use by oral route.

Adults

The recommended dose is generally 12.5 mg every 4-6 hours or 25 mg every 8 hours, depending on the type and severity of pain. The total daily dose should not exceed 75 mg.

The lowest effective dose should be used for the shortest duration necessary to control symptoms in order to minimize unwanted effects (see section 4.4).

KETAVEL should not be considered for long-term use, and treatment should be limited to the symptomatic period.

Method of administration

Like all NSAIDs, KETAVEL should preferably be taken with food or after meals. However, as food can delay the absorption of the drug (see Pharmacokinetic properties), it is recommended to take it at least 30 minutes before meals in cases of acute pain.

Additional information on special populations

Renal impairment

In patients with mild renal dysfunction (creatine clearance 60-89 ml/min) the starting dose should be reduced to a total daily dose of 50 mg. KETAVEL should not be used in patients with moderate to severe renal dysfunction (creatine clearance < 59 ml/min) (see section 4.3).

Hepatic impairment

Patients with mild or moderate hepatic dysfunction should start treatment at low doses (50 mg total daily dose) and should be closely monitored. KETAVEL should not be used in patients with severe hepatic dysfunction.

Pediatric population

There are no studies of dexketoprofen in children and adolescents. Therefore, its safety and efficacy have not been established in this age group. KETAVEL should not be used in children and adolescents.

Geriatric population

In elderly patients, treatment should start with the lowest dose range (50 mg total daily dose). After confirming good tolerance, dose can be increased to the amounts recommended for general population.

4.3. Contraindications

KETAVEL is contraindicated in:

- Patients with allergy to dexketoprofen, other NSAIDs, or any excipient listed in section 6.1.
- Patients who experience asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylaxis-like reactions associated with NSAIDs have been reported in these patients (see section 4.4).
- Patients with a history of photoallergic/phototoxic reactions during ketoprofen or fibrates therapy.
- Patients with active or suspected peptic ulcer/bleeding, or those with a history of recurrent peptic ulcers/gastrointestinal hemorrhage, gastrointestinal bleeding, ulceration, or perforation.
- Patients with chronic dyspepsia.
- Patients with a history of gastrointestinal bleeding or perforation of previous NSAID therapy.
- Patients with active bleeding or bleeding disorders.
- Patients with Crohn's disease or ulcerative colitis.
- Patients with severe heart failure.
- Patients with moderate or severe renal impairment (creatinine clearance < 59 ml/min).
- Patients with severe hepatic impairment (Child-Pugh category 10-15).
- Patients with hemorrhagic diathesis or other clotting disorders.
- Patients with severe dehydration (due to vomiting, diarrhea, or inadequate fluid intake).
- During the third trimester of pregnancy and while breastfeeding (see section 4.6).
- KETAVEL is contraindicated for perioperative pain treatment in coronary artery bypass graft (CABG) surgery (see section 4.4).

4.4. Special warnings and precautions for use

Warnings

Cardiovascular Risk:

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

Gastrointestinal (GI) Risk:

- NSAIDs can cause severe and potentially fatal adverse GI effects such as bleeding, ulceration, and perforation of the stomach or intestines. These adverse events can occur at any time, with or without warning symptoms. Elderly patients are at a higher risk of serious GI effects (see Warnings).

The safety of use in children and adolescents has not been established.

Caution should be exercised when using the drug in patients with a history of allergic conditions.

Concurrent use of KETAVEL with other NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Adverse effects can be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2 and the gastrointestinal and cardiovascular risks below).

Gastrointestinal (GI) Effects - Risk of Ulceration, Bleeding, or Perforation

At any stage of treatment, whether or not there are warning symptoms or a history of serious GI events, NSAIDs, including KETAVEL, may cause potentially fatal GI adverse effects such as inflammation or bleeding in the stomach, small intestine, or large intestine. If gastrointestinal bleeding or ulceration occurs in patients taking KETAVEL, the treatment should be discontinued.

Only one in five patients who develop a serious GI adverse event while on NSAID therapy exhibits symptoms. It has been observed that upper GI ulcers, major bleeding, or perforations occur in approximately 1% of patients treated for 3 to 6 months and in about 2-4% of patients treated for one year. These trends may persist with long-term treatment, increasing the likelihood of a serious GI event at any point in the patient's therapy. However, even short-term treatment is not without risk.

Patients using NSAIDs with a history of peptic ulcer and/or GI bleeding have a 10-fold higher risk of developing GI bleeding compared to those without these risk factors. Other factors that may increase the risk of GI bleeding in patients treated with NSAIDs include treatment with oral corticosteroids or anticoagulants, prolonged use of NSAIDs, smoking, alcohol consumption, advanced age, and poor general health.

In patients with a history of ulcers complicated by bleeding or perforation (see Section 4.3), in debilitated individuals, and in the elderly, the risk of gastrointestinal bleeding, ulceration, or perforation increases with higher NSAID doses.

To minimize the potential risk of an adverse GI event, patients should be treated with the lowest effective dose of NSAIDs for the shortest duration possible. Both patients and healthcare providers should remain vigilant for signs and symptoms of GI ulceration and bleeding during NSAID therapy. If a serious GI event is suspected, additional evaluation and treatment should be promptly initiated. If the adverse event does not resolve, NSAID therapy should be discontinued. Alternative therapies not involving NSAIDs should be considered for high-risk patients.

Elderly Patients: The frequency of adverse reactions to NSAIDs, particularly GI bleeding and perforation, which can be fatal, is higher in the elderly (see Section 4.2). These patients should begin treatment at the lowest effective dose.

As with all NSAIDs, a history of esophagitis, gastritis, and/or peptic ulcer should be investigated, and complete healing ensured before initiating treatment with dexketoprofen trometamol. Patients with GI symptoms or a history of GI disease should be closely monitored for digestive disorders, particularly GI bleeding.

Treatment with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, as well as for those requiring concurrent low-dose aspirin or other drugs likely to increase GI risk (see below and Section 4.5).

Patients with a history of GI toxicity, especially elderly individuals, should report any unusual abdominal symptoms (particularly GI bleeding) at the early stages of treatment.

Caution is advised in patients taking oral corticosteroids, anticoagulants like warfarin, selective serotonin reuptake inhibitors, or antiplatelets like aspirin concurrently, as these may increase the risk of ulceration or bleeding (see Section 4.5).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time through the inhibition of prostaglandin synthesis. Therefore, the use of dexketoprofen trometamol is not recommended in patients undergoing treatment with warfarin or other coumarins, or heparins, which affect hemostasis.

Renal Effects

Long-term NSAID use can lead to renal papillary necrosis and other renal damage. Additionally, since renal prostaglandins play a compensatory role in maintaining renal perfusion, renal toxicity has been observed in certain patients. Administering NSAIDs to these individuals can cause a dose-dependent decrease in prostaglandin synthesis and, consequently, renal blood flow, accelerating renal decompensation. Patients at high risk for such reactions include those with impaired renal function, heart failure, liver dysfunction, those using diuretics or angiotensin-converting enzyme (ACE) inhibitors, and the elderly.

Following the discontinuation of NSAID therapy, renal function typically returns to baseline.

Like all NSAIDs, KETAVEL can increase plasma urea nitrogen and creatinine levels. Similar to other prostaglandin synthesis inhibitors, it may be associated with adverse renal effects, such as glomerulonephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, and renal dysfunction.

KETAVEL should be used cautiously in patients with hematopoietic disorders, systemic lupus erythematosus, or mixed connective tissue diseases. Like other NSAIDs, dexketoprofen may mask symptoms of infectious diseases.

Caution is advised in patients with renal impairment. NSAID use in such patients may result in worsening renal function, fluid retention, and edema. Care should also be taken in patients receiving diuretic therapy or those at risk of hypovolemia, which may increase nephrotoxicity risk.

Advanced Renal Diseases

KETAVEL is contraindicated in patients with moderate to severe renal dysfunction (creatinine clearance <59 ml/min).

Caution is advised in patients with hepatic dysfunction.

Like other NSAIDs, dexketoprofen may cause temporary, mild increases in certain liver parameters and significant increases in SGOT and SGPT. If drug-related increases in these parameters are observed, treatment should be discontinued.

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials lasting up to three years with selective and non-selective COX-2 inhibitors have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Both selective and non-selective COX-2 inhibitors carry similar risks. Patients with existing cardiovascular disease or risk factors for cardiovascular disease may be at higher risk. To minimize the likelihood of adverse cardiovascular events in patients receiving NSAIDs, the lowest effective dose should be used for the shortest duration possible. Even in the absence of prior cardiovascular symptoms, both physicians and patients should remain alert for the development of such events. Patients should be informed beforehand about the symptoms and signs of serious cardiovascular events and the actions to take should they occur.

There is no consistent evidence that concurrent aspirin use reduces the increased risk of serious cardiovascular thrombotic events associated with NSAID use. The concomitant use of NSAIDs and aspirin increases the risk of serious gastrointestinal (GI) events.

In two large controlled clinical trials involving the use of a selective COX-2 NSAID for pain management in the first 10-14 days following coronary artery bypass grafting (CABG) surgery, an increased incidence of myocardial infarction and stroke was observed (see Section 4.3 Contraindications). KETAVEL is contraindicated for perioperative pain management in patients undergoing CABG surgery.

Patients with uncontrolled hypertension, heart failure, diagnosed ischemic heart disease, peripheral artery disease, and/or cerebrovascular disease should be carefully evaluated before being treated with

dexketoprofen trometamol. The same caution should be applied before starting long-term treatment in patients with cardiovascular risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking).

Hypertension
Like all NSAIDs, dexketoprofen can cause the development of hypertension or worsen pre-existing hypertension, both of which can increase cardiovascular events risk. Patients treated with thiazide diuretics or loop diuretics may experience reduced response to diuretic therapy when using NSAIDs. NSAIDs, including dexketoprofen, should be used with caution in hypertensive patients. Blood pressure should be closely monitored at the start of treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Some patients treated with NSAIDs, including dexketoprofen, experienced fluid retention and edema. Therefore, dexketoprofen should be used with caution in patients with fluid retention or heart failure.

Skin Reactions
Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which can be fatal, have been reported with the use of NSAIDs, including dexketoprofen (see Section 4.8). These severe events can occur without warning. The highest risk of such reactions is observed at the beginning of treatment, and many of these reactions occur within the first month of therapy. Patients should be informed in advance about the signs and symptoms of serious skin reactions, and if symptoms such as skin itching, mucosal lesions, or other signs of hypersensitivity appear, KETAVEL should be discontinued immediately.

As an exception, chickenpox 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 overlooked. Therefore, the use of KETAVEL is not recommended in the case of chickenpox.

Anaphylactoid reactions
As with other NSAIDs, anaphylactoid reactions may occur with dexketoprofen in some patients whose previous exposure to the drug is unknown. KETAVEL should not be administered to patients with aspirin triad (a condition known as analgesic intolerance or acetylsalicylic acid intolerance in asthmatic patients). This symptom complex typically arises in asthmatic patients with or without nasal polyps who experience severe and potentially fatal bronchospasm after using aspirin or NSAIDs. (See section 4.3 and section 4.4 Special warnings and precautions for use - Pre-existing asthma). In the case of an anaphylactoid reaction, immediate medical attention should be sought.

Pregnancy
As with other NSAIDs, dexketoprofen should not be used during the third trimester of pregnancy because it may cause early closure of the ductus arteriosus (the opening between the aorta and the pulmonary artery that should close after birth). KETAVEL is contraindicated in the third trimester of pregnancy and during lactation.

Precautions
General
Dexketoprofen should not be expected to replace corticosteroids or treat their deficiency. Sudden withdrawal of corticosteroids may lead to exacerbation of the disease. Patients undergoing long-term corticosteroid treatment should gradually reduce their treatment if discontinuation is decided.

The pharmacological activity of KETAVEL in reducing fever and inflammation may reduce the usefulness of diagnostic signs used in detecting complications of painful conditions that are considered non-infectious.

Hepatic effects

In patients receiving NSAIDs, including dexketoprofen, up to 15% may experience elevations in one or more liver tests to the upper limit. These laboratory anomalies may progress, remain unchanged, or resolve spontaneously when treatment continues. In clinical studies with NSAIDs, serious increases in ALT and AST activities (three times the normal upper limit or more) have been reported in about 1% of patients. In addition, rarely, severe hepatic reactions such as jaundice, fatal fulminant hepatitis, liver necrosis, and liver failure have been reported, some of which have been fatal.

In patients with symptoms indicative of liver dysfunction or abnormal liver test results, dexketoprofen treatment should be assessed for the potential development of more severe hepatic reaction events. If abnormal liver function tests persist or worsen, or if clinical signs or symptoms of liver disease develop, or other symptoms (e.g., eosinophilia, skin rashes, etc.) occur, treatment with KETAVEL should be discontinued and appropriate tests should be conducted.

Hematological effects

Patients on NSAIDs, including dexketoprofen, may sometimes have anemia. This could be due to fluid retention, hidden or apparent gastrointestinal blood loss, or an effect on erythropoiesis that is not fully identified. Patients receiving long-term treatment with NSAIDs, including dexketoprofen, should regularly monitor hemoglobin and hematocrit levels if they show any anemia signs or symptoms.

NSAIDs have been shown to inhibit platelet aggregation in some patients, prolonging bleeding time. Unlike aspirin, their effect on platelet function is quantitatively less, shorter in duration, and reversible. Patients with a history of coagulation disorders or those on anticoagulant therapy, who may experience adverse effects due to changes in platelet function, must be closely monitored when using KETAVEL.

Pre-existing asthma

Asthma patients may have aspirin-sensitive asthma. In patients with aspirin sensitivity, the use of aspirin has been associated with severe bronchospasm, which can be fatal. Since cross-reactions, including bronchospasm, have been reported between aspirin and other NSAIDs in these patients, KETAVEL should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Laboratory tests

Since serious gastrointestinal ulcers and bleeding may occur without warning symptoms, physicians should monitor patients for signs or symptoms of gastrointestinal bleeding. Patients receiving long-term NSAID treatment should have complete blood counts and biochemical profiles checked periodically. If clinical signs or symptoms compatible with liver or renal disorders develop, or if systemic symptoms (e.g., eosinophilia, rashes, etc.) appear, or if liver function tests become abnormal or worsen, treatment with KETAVEL should be discontinued.

4.5. Interaction with other medicinal products and other forms of interaction

Following interactions are usually applicable to all non-steroidal anti-inflammatory drugs (NSAIDs):

Combinations not recommended:

- Other NSAIDs (including high doses silicates ≥ 3 g/day): Gastrointestinal ulcers and bleeding may increase due to synergistic effects, so the simultaneous use of several NSAIDs should be avoided.
- Anticoagulants: NSAIDs can enhance the effects of anticoagulants such as warfarin (see Section 4.4) due to dexketoprofen's high plasma protein binding, inhibition of platelet function, and gastroduodenal mucosal damage. If this combination cannot be avoided, close clinical monitoring and laboratory follow-up should be performed.
- Heparins: The risk of hemorrhage increases (due to inhibition of platelet function and gastroduodenal mucosal damage). If the combination cannot be avoided, close clinical monitoring and laboratory follow-up should be performed.
- Corticosteroids: There is increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).

- Lithium (identified with many NSAIDs): NSAIDs increase blood lithium levels (by reducing renal excretion of lithium), which may lead to toxic levels. Therefore, this parameter should be monitored during the initiation, dose adjustment, and discontinuation of dexketoprofen treatment.
- Methotrexate, when used in doses of 15 mg/week or higher: There is generally an increased risk of hematologic toxicity due to reduced renal clearance of methotrexate when used with anti-inflammatory agents.
- Hydantoins and sulfonamides: Toxic effects of these compounds may be increased.

Combinations Requiring Precaution:

– Diuretics, ACE inhibitors, antibacterial aminoglycosides, and angiotensin II receptor antagonists: Dexketoprofen may reduce the effect of diuretics and antihypertensive products. In patients with compromised kidney function (e.g., dehydrated patients or elderly patients with compromised kidney function), the combined use of cyclooxygenase inhibitors, ACE inhibitors, angiotensin II receptor antagonists, or antibacterial aminoglycosides may further impair kidney function, which is usually reversible. In cases where a diuretic and dexketoprofen are prescribed together, it should be ensured that the patients are sufficiently hydrated, and renal functions should be monitored at the start of treatment.
– Methotrexate use at doses lower than 15 mg/week: The hematological toxicity of methotrexate increases, typically due to reduced renal clearance by anti-inflammatory compounds. In the first weeks of the combination, blood counts should be monitored weekly. Monitoring should be increased in cases of mild renal impairment and in elderly patients.
– Pentoxifylline: Increased risk of bleeding. Clinical monitoring should be increased, and bleeding time should be checked more frequently.
– Zidovudine: After starting NSAIDs, there is a risk of severe anemia and increased red blood cell toxicity due to the effect on reticulocytes. Complete blood count and reticulocyte count should be monitored one to two weeks after starting NSAID treatment.
– Sulfonylureas: NSAIDs can increase the hypoglycemic effects of sulfonylureas by displacing them from plasma protein binding sites.

Combinations to be cautious with:

– Beta-blockers: Treatment with an NSAID may reduce the antihypertensive effects by inhibiting prostaglandin synthesis.
– Cyclosporine and tacrolimus: NSAIDs may increase nephrotoxicity through renal prostaglandin-mediated effects. Renal functions should be calculated during combination therapy.
– Thrombolytics: Increased risk of bleeding.
– Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
– Probenecid: Plasma concentrations of dexketoprofen may increase; this interaction may be due to an inhibitory mechanism in the renal tubular secretion area and glucuronidation, and it may require adjustment of the dexketoprofen dose.
– Cardiac glycosides: NSAIDs may increase plasma glycoside levels.
– Mifepristone: Since prostaglandin synthetase inhibitors theoretically pose a risk of altering mifepristone's effectiveness, NSAIDs should not be used within 8-12 days after mifepristone administration.
– Quinolone Antibiotics: Data from animal studies suggest that the combined use of NSAIDs and high doses of quinolones may increase the risk of convulsions.

4.6. Fertility, pregnancy and lactation

General principles

Pregnancy category is “C” in the 1st and 2nd trimesters and is “D” in the 3rd trimester.

Women of childbearing potential / Contraception in males and females
No data is available regarding contraception.

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

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Epidemiological data have raised concerns regarding the increased risk of miscarriage, heart malformations, and gastroschisis following the use of prostaglandin synthesis inhibitors in the early stages of pregnancy. The absolute risk of cardiovascular malformations has increased from less than 1% to approximately 1.5%. It is believed that the risk increases with treatment dose and duration.

In the first and second trimesters of pregnancy, dexketoprofen trometamol should not be administered unless clearly necessary. If dexketoprofen trometamol is used by a woman trying to conceive or in the first and second trimesters of pregnancy, the dose should be kept as low as possible and the treatment duration should be as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may have the following effects on the fetus:
- Cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction leading to renal failure with oligohydramnios;

At the end of pregnancy, for the mother and newborn:
- The possibility of prolonged bleeding time, which can occur even at very low doses due to an anti-aggregant effect;
- Inhibition of uterine contractions, which may cause delayed or prolonged labor.

Lactation Period
It is not known whether dexketoprofen passes into breast milk (see Section 4.3 Contraindications).

Fertility
Like other NSAIDs, the use of dexketoprofen trometamol may affect fertility and is not recommended for women trying to conceive. The discontinuation of dexketoprofen trometamol should be considered in women having difficulty getting pregnant or who are being investigated for infertility. Dexketoprofen trometamol 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
Since fatigue and dizziness may occur, KETAVEL tablets may have a mild to moderate effect on the ability to drive and use machines.

4.8. Undesirable effects
In clinical studies, the undesirable effects that were at least possibly associated with dexketoprofen trometamol and reported after the marketing of dexketoprofen are listed below in a table, classified by system organ class and frequency.

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				Neutropenia, thrombocytopenia
Immune system disorders			Laryngeal edema	Anaphylactic reaction, including anaphylactic shock
Metabolism and nutrition disorders			Anorexia	
Psychiatric disorders		Insomnia anxiety		
Nervous system disorders		Headache, dizziness, somnolence	Paresthesia, syncope	
Eye disorders				Blurred vision
Ear and inner ear disorders		Vertigo		Tinnitus
Cardiac disorders		Palpitations		Tachycardia
Vascular disorders		Facial flushing	Hypertension	Hypotension
Respiratory, thoracic disorders, and mediastinal			Bradypnea	Bronchospasm, dyspnea
Gastrointestinal disorders	Nausea and/or vomiting, abdominal pain, diarrhea, dyspepsia	Gastritis, constipation, dry mouth, flatulence	Peptic ulcer, peptic ulcer bleeding or perforation (see section 4.4.)	Pancreatitis
Hepatobiliary disorders			Hepatitis	Hepatocellular damage
Skin and subcutaneous tissue disorders		Skin rashes	Urticaria, acne, increased sweating	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome), angioedema, facial edema, photosensitivity reactions, itching

Musculoskeletal, connective tissue, and bone disorders			Back pain	
Kidney and urinary tract disorders			Acute renal impairment, polyuria	Nephritis or nephrotic syndrome
Reproductive system and breast disorders			Menstrual disorders; prostatic disorders	
General disorders and administration site conditions		Fatigue, pain, asthenia, rigor, malaise	Peripheral edema	
Investigations			Abnormal liver function test	

Gastrointestinal: The most commonly observed adverse events are gastrointestinal. Sometimes, fatal peptic ulcers, perforation, or gastrointestinal bleeding may occur, especially in the elderly (see Section 4.4). Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, colitis, and worsening of Crohn's disease (see Section 4.4 Special warnings and precautions for use) have been reported after use. Less frequently, gastritis has been observed. Edema, hypertension, and cardiac disorders have been reported related with NSAID therapy.

As with other NSAIDs, the following adverse effects may occur:
Aseptic meningitis, particularly more common in those with systemic lupus erythematosus or mixed connective tissue disease; hematological reactions (purpura, aplastic and hemolytic anemia, and rarely agranulocytosis and marrow hypoplasia).

Bullous reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (very rare).
Clinical trials and epidemiological data suggest that the use of some NSAIDs (especially at high doses and prolonged treatment) may be associated with a small increase in the risk of arterial thrombotic events (particularly 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 via the national reporting system.

4.9. Overdose
The symptoms following overdose are not well known. Similar medicinal products have caused gastrointestinal (vomiting, anorexia, abdominal pain) and neurological (drowsiness, dizziness, disorientation, headache) disturbances.

In case of accidental ingestion or overdose, symptomatic treatment should be applied immediately, depending on the patient's clinical condition. Activated charcoal should be administered within one hour if an adult or child has ingested more than 5 mg/kg. Dextropropoxyphene trometamol can be removed from the body by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group : Propionic acid derivatives
ATC Code : M01AE17

Dexketoprofen trometamol is the trometamol salt of S-(+)-2-(3-benzoylphenyl) propionic acid, a drug in the non-steroidal anti-inflammatory drug (NSAID) group (M01A) with analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of NSAIDs involves the inhibition of the cyclooxygenase pathway, which reduces prostaglandin synthesis. Specifically, the inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG2 and PGH2, which form prostaglandins PGE1, PGE2, PGF2α, PGD2, and also prostacyclin PGI2 and thromboxanes (TxA2 and TxB2), is involved. Additionally, the inhibition of prostaglandin synthesis affects other inflammation mediators, such as kinins, resulting in an indirect effect in addition to the direct effect.

In animal and human studies, dexketoprofen has been shown to inhibits COX-1 and COX-2 activities.

Clinical studies in various pain models have shown that dexketoprofen trometamol has a significant analgesic effect. The onset of analgesic effect was observed within 30 minutes after administration in some studies. The analgesic effect lasts for 4-6 hours.

5.2. Pharmacokinetic properties

General Properties

Absorption

After oral administration of dexketoprofen trometamol to humans, Cmax is reached 30 minutes later (range 15-60 minutes). When taken with food, the AUC (area under the curve) remains unchanged, however, the Cmax of dexketoprofen trometamol decreases and the absorption rate is delayed (increased T_{max}).

Distribution

The distribution and elimination half-life of dexketoprofen trometamol are 0.35 and 1.65 hours, respectively. Like other drugs that bind extensively to plasma proteins (99%), the average volume of distribution is low at 0.25 L/kg.

Biotransformation and Elimination

After the administration of dexketoprofen trometamol, only the S-(+) enantiomer is found in the urine, indicating no conversion to the R-(-) enantiomer in humans. In multiple-dose pharmacokinetic studies, it was observed that the AUC after the last dose was similar to that obtained after a single dose, suggesting no drug accumulation.

The main route of elimination of dexketoprofen is renal excretion following glucuronidation.

Linearity/non-linearity

Dexketoprofen trometamol shows linear pharmacokinetics with a dose-dependent increase in systemic exposure following oral administration.

5.3. Preclinical safety data

Preclinical data, based on classical studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and immunopharmacology, has not shown any specific danger to humans. Chronic toxicity studies conducted on mice and monkeys identified the No Observed Adverse Effect Level (NOAEL) as 3 mg/kg/day. The main undesirable effect observed at high doses were gastrointestinal erosions and ulcers that developed in a dose-dependent manner.

In animals, it has been shown that the administration of a prostaglandin synthesis inhibitor leads to an increase in pre- and post-implantation losses and embryo-fetal death. Additionally, an increased incidence of various malformations, including cardiovascular, was reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. However, animal studies with dexketoprofen trometamol did not show reproductive toxicity (see Section 5.3).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cornstarch
Microcrystalline cellulose (Type 101)
Sodium starch glycolate (Type A)
Glycerol monostearate
Microcrystalline cellulose (Type 102)

Sheffcoat White PVA 02 5X00737
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol 3350
Polyethylene glycol 8000
Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 30°C.

6.5. Nature and contents of container

Opaque PVC/PE/PVDC – aluminum foil blisters are used. The blisters are packed in cardboard boxes.
The box is supplied with a user package leaflet and contains blister packs of 20 or 30 tablets.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)

2014/854

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization : 04.12.2014

Date of latest renewal :

10. DATE OF REVISION OF THE SPC