

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ELEKTRA® FORT 50 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each film coated tablet contains 73.8 mg dexketoprofen trometamol equivalent to 50 mg dexketoprofen.

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

White, round, biconvex film coated tablet scored on one side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and for the treatment of acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea.

4.2. Posology and method of administration

Posology / frequency and duration of administration

For oral use.

Adults

According to the nature and severity of pain, the recommended dosage is generally 75 mg (25 mg every 8 hours [1/2 film coated tablet]). The total daily dose should not exceed 75 mg.

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

ELEKTRA® FORT is not intended for long term use and the treatment must be limited to the symptomatic period.

Method of application

Like all NSAIDs, ELEKTRA® FORT should be taken preferably with food or after meals. However, concomitant administration with food delays the absorption rate of the drug (see Pharmacokinetic Properties), thus in case of acute pain it is recommended that administration is at least 30 minutes before meals.

Additional information on special populations**Renal failure:**

The initial dosage should be reduced to 50 mg total daily dose in patients with mildly impaired renal function (creatinine clearance 60 - 89 ml / min). ELEKTRA® FORT should not be used in patients with moderate to severe renal dysfunction (creatinine clearance <59 ml / min) (see section 4.3).

Hepatic failure:

Patients with mild to moderate hepatic dysfunction should start therapy at reduced doses (50 mg total daily dose) and be closely monitored. ELEKTRA® FORT should not be used in patients with severe hepatic dysfunction.

Pediatric population

Dexketoprofen has not been studied in children and adolescent. Therefore the safety and efficacy in children and adolescents have not been established. It should not be used in children and adolescent.

Geriatric Population

In elderly patients it is recommended to start the therapy at the lower end of the dosage range (50 mg total daily dose). The dosage may be increased to that recommended for the general population only after good general tolerance has been ascertained.

4.3. Contraindications

ELEKTRA® FORT must not be administered in the following cases:

- Patients hypersensitive to the active substance, to any other NSAIDs, or to any of the excipients (listed in section 6.1),
- Patients with asthma, urticaria, or allergic reactions due to the use of aspirin or other NSAIDs. Severe, rarely fatal, anaphylaxis-like reactions due to NSAIDs have been reported in such patients (see section 4.4).
- Known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates
- Patients with active or suspected peptic ulcer/gastrointestinal hemorrhage or any history of gastrointestinal bleeding, ulceration or perforation,
- Patients with chronic dyspepsia.
- Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

- Patients who have other active bleedings or bleeding disorders.
- Patients with Crohn's disease or ulcerative colitis.
- Patients with severe heart failure,
- Patients with moderate to severe renal dysfunction (creatinine clearance ≤ 59 ml/min).
- Patients with severely impaired hepatic function (Child-Pugh score 10 - 15).
- Patients with hemorrhagic diathesis and other coagulation disorders.
- Patients with severe dehydration (caused by vomiting, diarrhea or insufficient fluid intake)
- During the third trimester of pregnancy and lactation period (see section 4.6).
- ELEKTRA® FORT is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4.).

4.4. Special warnings and precautions for use

Warnings

Cardiovascular risk:

-NSAIDs may cause an increased risk of 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).

-ELEKTRA® FORT is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Warnings).

Gastrointestinal (GI) risk:

NSAIDs are associated with GI adverse effects such as bleeding, ulceration, gastrointestinal perforation which can be fatal. These adverse events can occur at any time with or without prior warning symptoms. The elderly are at higher risk for serious GI effects (see Warnings).

The safety of use in children and adolescents has not been established. Caution is advised in patients with a history of allergic conditions.

The concomitant use of ELEKTRA® FORT with other 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 GI and cardiovascular risks below).

Gastrointestinal (GI) effects-ulceration, bleeding or perforation risk:

NSAIDs including ELEKTRA® FORT may cause gastrointestinal bleeding, ulceration or perforation which can be fatal, 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 ELEKTRA[®] FORT, the treatment should be withdrawn.

Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross 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. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation (see section 4.3), in weak patients and in the elderly.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). These patients should commence treatment on the lowest dose available.

As with all NSAIDs, any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with dexketoprofen trometamol. Patients with gastrointestinal symptoms or history of gastrointestinal disease should be monitored for digestive disturbances, especially gastrointestinal bleeding.

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 below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) especially 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 antiplatelet agents such as aspirin (see section 4.5).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time via inhibition of prostaglandin synthesis. Therefore, the use of dexketoprofen in patients who are receiving other therapy that interferes with haemostasis, such as warfarin or other coumarins or heparins is not recommended.

Renal effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID 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 ACE inhibitors, and the elderly.

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

As with all NSAIDs, ELEKTRA[®] FORT can increase plasma urea nitrogen and creatinine.

As with other inhibitors of prostaglandin synthesis, it can be associated with adverse effects on the renal system which can lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure.

ELEKTRA[®] FORT should be administered with caution to patients suffering from haematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease. As other NSAIDs, dexketoprofen can mask the symptoms of infectious diseases.

Caution should be exercised in patients with impairment of renal functions. In these patients, the use of NSAIDs may result in deterioration of renal function, fluid retention and oedema. Caution is also required in patients receiving diuretic therapy or those who could develop hypovolaemia as there is an increased risk of nephrotoxicity.

Advanced Renal Disease

ELEKTRA[®] FORT is contraindicated in patients with moderate to severe renal dysfunction (creatinine clearance < 59 ml/min).

Caution should be exercised in patients with impairment of hepatic functions.

As with other NSAIDs, it can cause transient small increases in some liver parameters, and also significant increases in SGOT and SGPT. In case of a relevant increase in such parameters, therapy must be discontinued.

Cardiovascular effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take 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 does 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). ELEKTRA[®] FORT is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic 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 longer-term treatment of the patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Hypertension:

Like all NSAIDs, dexketoprofen can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including dexketoprofen, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

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 fluid retention or heart failure.

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). These serious events may occur without warning. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and use of ELEKTRA® FORT should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ELEKTRA® FORT in case of varicella.

Anaphylactoid reactions:

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to dexketoprofen. ELEKTRA® FORT should not be given to patients with the aspirin triad (The analgesic intolerance or acetylsalicylic acid intolerance (ASAI) seen in asthmatic patients is called “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 section 4.3 and section 4.4 Special warnings and precautions for use - preexisting asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Pregnancy

As with other NSAIDs, dexketoprofen should not be used during the third trimester of pregnancy, because it may cause premature closure of the ductus arteriosus (an aperture between the two major arteries [the aorta and the pulmonary artery] that is open in the mother's womb and need to be closed following delivery). ELEKTRA® FORT is contraindicated during the third trimester of pregnancy and lactation.

Precautions**General:**

Dexketoprofen cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

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

Hepatic effects:

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, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs.

In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with dexketoprofen. If abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or other signs occur (e.g., eosinophilia, rash, etc.), ELEKTRA[®] FORT should be discontinued and appropriate tests should be requested.

Hematological Effects:

Anemia is sometimes seen in patients receiving NSAIDs, including dexketoprofen. This may be due to fluid retention, occult or gross 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 if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ELEKTRA[®] FORT who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

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 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ELEKTRA[®] FORT 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. Patients on long-term treatment with NSAIDs should have their complete blood count and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, ELEKTRA[®] FORT should be discontinued.

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

The following interactions apply to non-steroidal anti-inflammatory drugs (NSAIDs) in general:

Inadvisable combinations:

- Other NSAIDs including high doses of salicylates (≥ 3 g/day): Concomitant use of several NSAIDs should be avoided as they may increase the risk of gastrointestinal ulcers and bleeding via a synergistic effect.
- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4), due to the high plasma protein binding of dexketoprofen and 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.
- 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: There is an 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 anti-inflammatory 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 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, 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.

- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by anti-inflammatory agents in general. Weekly monitoring of blood count during the first weeks of the combination. Increased surveillance in the presence of even mildly impaired renal function, as well as in the elderly.
- Pentoxifylline: increased risk of bleeding. Increase clinical monitoring and check bleeding time more often.
- Zidovudine: risk of increased red cell line toxicity via action on reticulocytes, with severe anaemia occurring one week after the NSAID is started. Check complete blood count and reticulocyte count one to two weeks after starting treatment with the NSAID.
- Sulfonylureas: NSAIDs can increase the hypoglycaemic 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.
- Cyclosporin 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 which 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 concentration.
- Mifepristone: Since there is a theoretical risk that prostaglandin synthetase inhibitors may alter the efficacy of mifepristone, NSAIDs should not be used within 8-12 days of the mifepristone uptake.
- 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

No interaction study has been performed in special populations.

Pediatric population

No interaction study has been performed in pediatric populations.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C for the first and second trimesters; D for the third trimester.

Women with childbearing potential / Contraception

No data is available on contraception.

Pregnancy

ELEKTRA[®] FORT is contraindicated during third trimester of pregnancy (see section 4.3). Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.

Data from epidemiological studies raise concern about 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.

During the first and second trimester of pregnancy, dexketoprofen should not be given unless clearly necessary. If dexketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

the mother and the neonate, 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 labour.

Lactation

It is not known whether dexketoprofen is excreted in human breast milk. (See section 4.3 Contraindications).

Reproduction 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 should be considered. During the first and second trimester of pregnancy, dexketoprofen trometamol should not be given unless clearly necessary.

4.7. Effects on ability to drive and use machines

ELEKTRA® FORT film coated may have mild to moderate effects on the ability to drive and to operate machines as dizziness or drowsiness may occur.

4.8. Undesirable effects

The adverse events reported as at least possibly related with dexketoprofen in clinical trials, as well as the adverse reactions reported after the marketing of ELEKTRA® FORT are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common ($\geq 1/100$ - $<1/10$)	Uncommon: ($\geq 1/1000$ - $<1/100$)	Rare ($\geq 1/10000$ - $<1/100$)	Very rare isolated reports ($<1/10000$)
Blood and lymphatic system disorders				Neutropenia, thrombocytopenia
Immune system disorders			Laryngeal oedema	Anaphylactic reaction, including anaphylactic shock
Metabolism and nutrition disorders			Anorexia	
Psychiatric disorders:		Insomnia, anxiety		
Nervous system disorders		Headache, dizziness, somnolence	Paraesthesia, syncope	
Eye disorders				Blurred vision
Ear and Labyrinth Disorders		Vertigo		Tinnitus
Cardiac disorders		Palpitations		Tachycardia
Vascular disorders		Flushing	Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders			Bradypnoea	Bronchospasm, dyspnoea
Gastrointestinal disorders	Nausea and/or vomiting, abdominal pain, diarrhoea, dyspepsia	Gastritis, constipation, dry mouth, flatulence	Peptic ulcer, peptic ulcer haemorrhage or peptic ulcer perforation (see	Pancreatitis

			section 4.4)	
Hepatobiliary disorders			Hepatitis	Hepatocellular injury
Skin and subcutaneous tissue disorders		Skin rash	Urticaria, acne, sweating increased	Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, facial oedema, photosensitivity reaction, pruritus
Musculoskeletal and connective tissue disorders			Back pain	
Renal and urinary disorders			Acute renal failure, polyuria	Nephritis or nephrotic syndrome
Reproductive system and breast disorders			Menstrual disorder, prostatic disorder	
General disorders and administration site conditions		Fatigue, pain, asthenia, rigors, malaise	Peripheral oedema	
Investigations			Liver function test abnormal	

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, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed. Oedema, hypertension and cardiac failure have been reported in association with NSAIDs 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; haematological reactions (purpura, aplastic and haemolytic anaemia, and rarely agranulocytosis and medullar hypoplasia).

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

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).

4.9. Overdose

The symptomatology 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, immediately institute symptomatic therapy according to the patient's clinical condition. Activated charcoal should be administered if more than 5 mg/kg has been ingested by an adult or a child within an hour. Dexketoprofen trometamol may be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Propionic acid derivatives

ATC Code: M01AE17

Dexketoprofen trometamol is the tromethamine salt of S-(+)-2-(3-benzoylphenyl)propionic acid, an analgesic, anti-inflammatory and antipyretic drug, which belongs to the non-steroidal anti-inflammatory group of drugs (M01A).

The mechanism of action of non-steroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of the cyclooxygenase pathway. Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG₂ and PGH₂, which produce prostaglandins PGE₁, PGE₂, PGF₂ α and PGD₂ and also prostacyclin PGI₂ and thromboxanes (TxA₂ and TxB₂). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action which would be additional to the direct action.

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

Clinical studies performed on several pain models demonstrated effective analgesic activity of dexketoprofen trometamol. The onset of the analgesic activity was obtained in some studies at 30 minutes post-administration. The analgesic effect persists for 4 to 6 hours.

5.2. Pharmacokinetic properties

General properties

Absorption:

After oral administration of dexketoprofen trometamol to humans, the C_{max} is reached at 30 min (range 15 to 60 min). When administered concomitantly with food, the AUC does not change, however the C_{max} of dexketoprofen decreases and its absorption rate is delayed (increased t_{max}).

Distribution:

The distribution half-life and elimination half-life values of dexketoprofen are 0.35 and 1.65 hours, respectively. As with other drugs with a high plasma protein binding (99%), its volume of distribution has a mean value below 0.25 l/kg.

Biotransformation and elimination:

After administration of dexketoprofen trometamol only the S-(+) enantiomer is obtained in urine, demonstrating that no conversion to the R-(-) enantiomer occurs in humans. In multiple-dose pharmacokinetic studies, it was observed that the AUC after the last administration is not different from that obtained following a single dose, indicating that no drug accumulation occurs.

The main elimination route for dexketoprofen is glucuronide conjugation followed by renal excretion.

Linearity / Non-linearity

Dexketoprofen trometamol showed linear pharmacokinetics following an oral dose, with a dose-related increase during systemic exposure.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity and immunopharmacology. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day. At higher doses, the main adverse effect observed were dose-dependent gastrointestinal erosions and lesions.

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. Nevertheless, animal studies with dexketoprofen haven't shown reproductive toxicity (see section 5.3).

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Microcrystalline cellulose

Maize starch

Sodium starch glycollate

Glycerol distearate

Magnesium stearate
Hypromellose
Titanium dioxide
Talc
Polyethylene glycol

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C, protecting from light.

6.5. Nature and contents of container

30 film coated tablets are packed in white opaque PVC/PE/PVDC/Al folio blisters, in a cardboard box with the patient information leaflet.

6.6. Special precautions for disposal of waste materials derived from medicinal product and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST APPROVAL/RENEWAL OF THE APPROVAL

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10. DATE OF REVISION OF THE TEXT

[To be completed nationally]