

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dexketoprofen Rowex 12.5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Dexketoprofen trometamol 18.45 mg corresponding to dexketoprofen 12.5 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets.

White, biconvex cylindric shaped unscored tablets embossed with DT1 on one side.

Tablet dimensions are: 3.4 mm x 7.1 mm $\pm$ 0.3 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of pain of mild to moderate intensity, such as musculo-skeletal pain, dysmenorrhoea, dental pain.

4.2 Posology and method of administration

Adults:

According to the nature and severity of pain, the recommended dosage is generally 12.5 mg every 4-6 hours or 25 mg every 8 hours. 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).

Dexketoprofen Rowex tablets are not intended for long term use and the treatment must be limited to the symptomatic period.

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.

Elderly:

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.

Hepatic dysfunction:

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

Renal dysfunction:

The initial dosage should be reduced to 50 mg total daily dose in patients with mildly impaired renal function (creatinine clearance 50 – 80 ml / min) (see section 4.4). Dexketoprofen Rowex tablets should not be used in patients with moderate to severe renal dysfunction (creatinine clearance <50 ml / min) (see section 4.3).

Children and adolescents:

Dexketoprofen Rowex tablets have not been studied in children and adolescents. Therefore, safety and efficacy have not been established and the product should not be used in children and adolescents.

4.3 Contraindications

Dexketoprofen Rowex tablets must not be administered in the following cases:

- patients hypersensitive to dexketoprofen, to any other NSAID, or to any of the excipients in section 6.1.
- patients in whom substances with a similar action (e.g. acetylsalicylic acid, or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema.
- patients with active or suspected peptic ulcer/haemorrhage or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) or chronic dyspepsia.
- patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- patients who have gastrointestinal bleeding or other active bleedings or bleeding disorders.
- patients with Crohn's disease or ulcerative colitis.
- patients with a history of bronchial asthma.
- patients with severe heart failure.
- patients with moderate to severe renal dysfunction (creatinine clearance <50 ml/min).
- patients with severely impaired hepatic function (Child-Pugh score 10 -15).
- patients with haemorrhagic diathesis and other coagulation disorders.
- during the third trimester of pregnancy and lactation period (see section 4.6).

4.4 Special warnings and precautions for use

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 Dexketoprofen Rowex with concomitant other NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised 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 bleeding, ulceration or perforation which can be fatal, have 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 Dexketoprofen Rowex, the treatment should be withdrawn. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly.

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.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

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 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, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet 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 trometamol in patients who are receiving other therapy that interferes with haemostasis, such as warfarin or other coumarins or heparins is not recommended (see Section 4.5).

As with all NSAIDs, it 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.

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.

Dexketoprofen Rowex tablets 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 hepatic and/or renal functions as well as in patients with a history of hypertension and/or heart failure. 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. Special caution should be exercised in patients with a history of cardiac disease, in particular those with previous episodes of heart failure as there is an increased risk of triggering heart failure.

Elderly patients are more likely to be suffering from impaired renal cardiovascular or hepatic function (see section 4.2).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Dexketoprofen Rowex should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 Rowex should not be used during first and second trimester of pregnancy unless clearly necessary.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAIDs 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.

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).

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 doses of salicylates (3 g/day): administration of several NSAIDs together 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 haemorrhage (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 haematological 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 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 (see section 4.4 Special warnings and special precautions for use).
- Methotrexate, used at low doses, less than 15 mg/week: increased haematological toxicity of methotrexate via a decrease in its renal clearance by antiinflammatory 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 Rowex 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 concentration.
- 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.

4.6 Fertility, pregnancy and lactation

Dexketoprofen is contraindicated during pregnancy and lactation (see section 4.3)

Pregnancy

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. 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 trometamol haven't shown reproductive toxicity (see 5.3). During the first and second trimester of pregnancy, Dexketoprofen trometamol should not be given unless clearly necessary. If Dexketoprofen trometamol 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.

Dexketoprofen Rowex tablets are contraindicated during third trimester of pregnancy and lactation (see section 4.3).

Fertility

The use of Dexketoprofen 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.

Lactation

It is not known whether dexketoprofen is excreted in human milk. It must be avoided the use of dexketoprofen during the lactation. Dexketoprofen is contraindicated during breast-feeding. (see section 4.3).

4.7 Effects on ability to drive and use machines

Dexketoprofen Rowex tablets can cause minor or moderate influence on the ability to drive and use machines due to the possibility of dizziness or drowsiness occurring.

4.8 Undesirable effects

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

SYSTEM ORGAN CLASS	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.01-0.1%)	Very rare /Isolated reports (<0.01%)
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 section 4.4)	Pancreatitis
Hepatobiliary disorders	---	---	Hepatitis	Hepatocellular injury
Skin and subcutaneous tissue disorders	---	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	---

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 disorders (vomiting, anorexia, abdominal pain) and neurological (somnolence, vertigo, disorientation, headache).

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, antiinflammatory and antipyretic drug, which belongs to the non-steroidal anti-inflammatory group of drugs (M01AE).

The mechanism of action of non-steroidal antiinflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of 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

After oral administration of dexketoprofen trometamol to humans, the C_{max} is reached at 30 min (range 15 to 60 min).

The distribution half-life and elimination half-life values of dexketoprofen trometamol 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. The main elimination route for dexketoprofen is glucuronide conjugation followed by renal excretion.

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.

When administered concomitantly with food, the AUC does not change, however the C_{max} of dexketoprofen trometamol decreases and its absorption rate is delayed (increased t_{max}).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction 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. The main adverse effect observed at high doses was gastrointestinal erosions and ulcers that developed dose-dependently.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core excipients

Maize starch,
microcrystalline cellulose,
sodium starch glycolate (type A),
glycerol distearate,

Coating excipients

hypromellose (E-464),
titanium dioxide (E-171),
macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30 °C. Keep the blister packs in the outer carton in order to protect from light.

6.5 Nature and contents of container

Tablets are provided in blister packs (PVC-PVDC/aluminium blister)

Dexketoprofen Rowex 12.5 mg film coated tablets – 10, 20, 30, 40, 50, 500 film-coated tablets/pack

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry,
Co. Cork,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/216/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th October 2013

10 DATE OF REVISION OF THE TEXT