SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

DOLARIT 300 mg film coated tablet

2. Qualitative and quantitative composition

Active ingredient: Each tablet contains Etodolac 300 mg.

Excipients: Each tablet contains 206.3 mg lactose monohydrate (derived from cow's milk), 6.7 mg sodium starch glicolate.

For the excipients: see section 6.1.

3. Pharmaceutical form

Film Tablet.

White, oblong, bi convex, flat film coated tablets on both sides and edges

4. Clinical properties

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology / frequency and duration of administration:

As with other NSAIDs, after observing the patient's response to initial treatment with etodolac, the dose and frequency should be adjusted according to the physician's recommendation and the needs of each patient.

The adult dose is between 300-1200 mg per day. The maximum daily dose should not exceed 1200 mg. It is used twice a day, morning and evening.

Route of administration

It is use by oral route . It should preferably be taken with or after meals.

Additional information on special populations:

Kidney failure:

There was no significant difference in total and free etodolac metabolism in patients with mild to moderate renal impairment (creatinine clearance 37-88 mL / min). In patients undergoing hemodialysis, there was a 50% increase in total etodolac clearance, since unbound fraction was 50% higher, and free etodolac clearance was unchanged. This shows the importance of protein binding in etodolac metabolism. Etodolac cannot be removed from the body by dialysis.

Liver failure:

Total and free etodolac metabolism did not change in patients with compensated liver cirrhosis. Although dose adjustment is not usually required in this patient group, etodolac clearance is dependent on liver function and can be reduced in patients with severe hepatic impairment.

Pediatric Population:

Etodolac has not been evaluated in pediatric patients in terms of efficacy and safety and is therefore not recommended for use in children.

Geriatric Population:

No dosage adjustment is required in elderly patients.

The risk of adverse reactions is high in elderly patients.

By using the lowest effective dose as soon as necessary to control symptoms, undesirable effects can be minimized. Patients should be monitored closely for the risk of gastrointestinal bleeding during NSAID treatment.

4.3 Contraindications

DOLARIT is contraindicated in patients known to be hypersensitive to etodolac or any substance contained in the tablet.

DOLARIT should not be used in patients who develop allergic reactions during treatment with aspirin or other non-steroidal anti-inflammatory drugs due to possible cross-drug reactions or in patients with a history of acute asthma, rhinitis, urticaria.

Also, it should not be used in patients with a history of gastrointestinal bleeding or perforation related to treatment with previous NSAIDs.

DOLARIT should not be used in patients with severe heart failure immediately before or after by-pass and heart surgery.

Etodolac is also contraindicated in patients with active peptic ulcer or in patients with a history of peptic ulcer disease (including gastrointestinal hemorrhage caused by other non-steroidal anti-inflammatory drugs).

Contraindicated in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular risk

- NSAIDs can cause potentially fatal increases in the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with the duration of use. This risk is highest in patients with cardiovascular disease or risk factors for cardiovascular disease.
- Etodolac is contraindicated for use as a pre- and post-operative pain reliever in patients undergoing coronary artery by-pass graft surgery.

Gastrointestinal risk

- NSAIDs can cause potentially fatal increases in the risk of serious gastrointestinal adverse effects such as bleeding, ulcers, perforation of the stomach or intestines. These effects may occur at any time during use, without warning symptoms. The elderly constitute the greatest risk group for serious gastrointestinal effects.

Warnings:

Cardiovascular thrombotic effects:

Many clinical studies with COX-2 selective and nonselective non-steroidal antiinflammatory (NSAID) drugs have been shown to have a high risk of fatal serious cardiovascular thrombotic events, myocardial infarction and paralysis.

All NSAIDs with and without COX-2 selective may have a similar risk. The risk may be higher in patients with known cardiovascular disease or with a risk factor for cardiovascular disease. In patients receiving NSAID drug therapy, the lowest effective dose should be used for the shortest period to minimize the risk of a potential adverse cardiovascular effect. Even if no cardiovascular symptoms have been seen before, patients and doctors should be careful about the occurrence of such events. Patients should be informed about the signs and / or symptoms of serious cardiovascular events and what to do if they occur.

There is no consistent evidence that concurrent use of aspirin reduces the risk of serious cardiovascular thrombotic events that increase with the use of NSAIDs.

Concurrent use of an NSAID with aspirin increases the risk of serious gastrointestinal effects (see Gastrointestinal effects).

Two large, controlled clinical trials using COX-2 selective NSAIDs for the treatment of pain in the first 10-14 days after coronary artery bypass surgery have shown an increased incidence of myocardial infarction and stroke (see Contraindications).

Hypertension:

Like other NSAIDs, DOLARIT can cause hypertension or worsen pre-existing hypertension, which may increase the incidence of cardiovascular events. When patients who are using thiazide or loop diuretics take NSAIDs, responses to these drugs may be impaired. All NSAIDs, including DOLARIT, should be used with caution in patients with hypertension. Blood pressure should be closely monitored at the beginning and throughout treatment of NSAIDs.

Congestive heart failure and edema:

Fluid retention and edema have been observed in some patients taking NSAIDs. DOLARIT should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal effects - Risk of ulceration, bleeding and perforation:

In patients treated with non-steroidal anti-inflammatory (NSAID) drugs, at any stage of treatment and without any warning symptoms; may cause serious gastrointestinal adverse effects in form of inflammation, bleeding, ulceration or perforation of the stomach, small intestine or large intestine which may result in death.

Only one in five patients with severe upper gastrointestinal complaints using NSAIDs is symptomatic. Severe upper gastrointestinal system ulcers, major hemorrhages or perforations associated with NSAID use have been shown to occur in approximately 1% of patients treated for 3-6 months and 2-4% of patients treated for one year. This tendency continue with prolongation of use and increase the likelihood of serious gastrointestinal adverse effects during the course of treatment. However, there is a risk even in short-term treatment.

NSAIDs should be used with caution in patients with a history of ulcer disease or gastrointestinal bleeding. Patients with a history of peptic ulcer disease and / or gastrointestinal bleeding and taking NSAIDs have a 10 times higher risk of developing gastrointestinal bleeding than those without any of these risk factors. The patients who NSAID drugs are applied to; concurrent use of oral corticosteroids or anticoagulants, prolonged NSAID drug therapy, smoking, alcohol use, aging and poor general health are other factors that increase the risk of gastrointestinal bleeding. The majority of spontaneous fatal gastrointestinal events are seen in elderly or impaired general health patients; therefore, particular attention should be exercised to the treatment of this population.

To minimize the risk of gastrointestinal adverse event potential in patients receiving NSAIDs, the lowest effective dose should be administered with shortest treatment duration. During NSAID drug therapy, patients and physicians should be careful for signs and symptoms of gastrointestinal ulceration and bleeding, and if there is a suspected severe gastrointestinal adverse effect, additional evaluation and treatment should be initiated immediately. This should include discontinuation of NSAID drug therapy until the severe gastrointestinal adverse effect is eliminated. Alternative therapies that do not include NSAIDs should be considered for high-risk patients.

Renal Effects

Long-term use of NSAIDs leads to renal papillary necrosis or other renal pathologies. Renal toxicity is also observed in patients in who renal prostaglandins play a compensatory role in achieving renal

perfusion. Administration of an NSAID to these patients may result in a dose-dependent decrease in prostaglandin production and renal blood flow, leading to significant renal decompensation. Patients at such risk; renal dysfunction, heart failure, liver dysfunction, use diuretic and ACE inhibitors and elderly patients. With the discontinuation of NSAID drug treatment, it is usually returned to the pre-treatment state.

Advanced Renal Disease

In controlled clinical trials, there is no information on the use of etodolac in patients with advanced kidney disease. Therefore, treatment with DOLARIT is not recommended in patients with advanced kidney disease. If treatment with DOLARIT is required, close monitoring of the patient's renal function is recommended.

Anaphylactoid Reactions

Anaphylactoid reactions may occur in patients who have not previously been treated with etodolac as with other NSAIDs. Etodolac; should not be given to the patients previously seen aspirin triad (asthma, urticaria or similar allergic reactions with aspirin or other NSAIDs).

More like, patients with bronchial asthma, vasomotor rhinitis and nasal polyposis may develop severe, fatal bronchospasm with aspirin or other NSAIDs. Fatal reactions have been reported in such patients (see Contraindications and Precautions - Pre-existing asthma). In such cases, emergency assistance should be provided.

Skin Reactions

NSAIDs including etodolac, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) which can be fatal. These serious events may occur without warning. Patients should be informed of the signs and symptoms of serious skin reactions and instructed to discontinue the drug at the appearance of a skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus.

Precautions

General

Etodolac is not used in place of corticosteroid or inadequate corticosteroid treatment. Sudden cessation of corticosteroids may exacerbate the disease. In patients undergoing long-term corticosteroid therapy, treatment should be reduced gradually if it is decided to stop corticosteroid therapy.

The pharmacological activity of etodolac in reducing inflammation (fever and) may reduce the usefulness of these diagnostic symptoms in monitoring the complications of presumed non-infectious, painful conditions.

Hepatic Effects

Nearly 15% of patients taking NSAIDs may have one or more liver function test limit increases and significant ALT and AST increases (approximately three times the upper limit of normal) in approximately 1% of patients receiving NSAIDs in clinical trials.).

These changes in laboratory findings may progress, remain unchanged, or may be transient despite continued treatment. Severe liver reactions such as jaundice and fatal fulminant hepatitis, liver necrosis and liver failure (some resulting in fatal) have been reported with the use of NSAIDs.

Patients with signs and / or signs of liver dysfunction or abnormal liver tests should be evaluated for evidence of more severe hepatic reactions when administering etodolac therapy. Etodolac therapy should be discontinued if clinical signs and symptoms consistent with liver disease occur or if systemic symptoms occur (eg rash, eosinophilia).

Hematological Effects

In patients using etodolac or other NSAIDs sometimes see anemia. This is because; fluid retention, latent or extensive gastrointestinal blood loss, or an unspecified effect on erythropoiesis. In patients with long-term use of NSAIDs including etodolac, if signs or symptoms are seen, hemoglobin or hematocrit values should be measured.

NSAIDs inhibit platelet aggregation and these agents have been shown to prolong bleeding in some patients. Unlike aspirin, its effects on platelet function are quantitatively less, shorter, and reversible. Patients treated with etodolac and having adverse effects on changes in platelet function (such as patients 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 leads to serious bronchospasm may be fatal. Etodolac should not be used in such patients because cross reactivity, including bronchospasm, has been reported among aspirin and other NSAIDs and caution should be exercised in patients with known asthma.

Information for Patients

Etodolac, like other NSAIDs, can cause serious cardiovascular side effects, such as myocardial infarction or stroke, which can result in hospitalization or even death. Although severe cardiovascular events can occur without stimulatory symptoms, patients should pay attention to signs and symptoms such as chest pain, shortness of breath, fatigue, speech pelting, and seek medical attention if they see any such signs or symptoms. The importance of this monitoring should be emphasized to patients (See Warnings - Cardiovascular thrombotic effects) .

Like other drugs in this class, etodolac can cause discomfort and rarely serious side effects such as gastrointestinal ulcers and bleeding, which may require hospitalization and may even be fatal.

As severe gastrointestinal system ulceration and bleeding can occur without any stimulating symptoms, doctors should warn patients undergoing chronic treatment to pay attention to the signs and symptoms of ulceration and bleeding, and epigastric pain, should be monitored for any signs or symptoms involving dyspepsia, melena, and hematemesis, and should inform them of the importance of this monitoring (see Warnings. Gastrointestinal effects - risk of ulceration, bleeding and perforation).

Etodolac, like other NSAIDs, can cause serious side effects, such as exfoliative dermatitis, Stevens Johnson syndrome and toxic epidermal necrolysis, which requiring hospitalization or may be fatal. Although severe skin reactions can occur without warning, patients should pay attention to skin rash and other hypersensitivity signs and symptoms, such as vesicles, fever or itching, and seek medical attention if they see any signs or symptoms. If any type of rash occurs in patients, they should be told to stop the drug immediately and consult their doctor as soon as possible.

Patients should be instructed to report unexplained weight gain or edema signs and symptoms to their physician immediately.

Patients should be informed about the signs and symptoms of hepatotoxicity (eg nausea, fatigue, lethargy, pruritis, jaundice, right upper quadrant sensitivity and flu-like syndrome). If this occurs, patients should be told to stop treatment and seek medical attention immediately.
Patients should also be instructed to seek immediate medical attention if an anaphylactoid reaction occurs (eg difficulty breathing, swelling of the face or throat) (see Warnings).
Etodolac, like other NSAIDs, should not be taken in the late stages of pregnancy; because it will cause premature closure of ductus arteriosus.
Laboratory Tests
Doctors should monitor the signs or symptoms of gastrointestinal bleeding, as severe gastrointestinal system ulceration and bleeding may occur without warning symptoms. As with other NSAIDs, full blood count and chemical profile of patients treated with long-term etodolac should be checked periodically for signs and symptoms of anemia.
Etodolac should be stopped if clinical signs and symptoms of liver disease occur, or if systemic symptoms (eosinophilia, rash, etc.) are detected, and if abnormal liver tests are detected, persist or worsen.
Each dose of this medicinal product contains less than 23 mg of sodium. No adverse effects due to sodium are expected.
Each tablet contains 206.3 mg of lactose monohydrate. Patients with rare hereditary galactose intolerance, Lapp lactose insufficiency or glucose-galactose malabsorption should not use this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin Converting Enzyme (ACE)-inhibitors: Studies shown that NSAIDs reduce the antihypertensive effects of ACE-inhibitor. This interaction should be considered in patients receiving NSAIDs and ACE inhibitors simultaneously.

Aspirin: When etodolac is co-administered with aspirin, protein binding decreases, but free etodolac clearance does not change. The clinical significance of this interaction is unknown. Even so, as with other NSAIDs, concomitant administration of etodolac and aspirin is generally not recommended due to the potential of increase side effects.

Furosemide: In clinical studies and post-marketing observations, etodolac may reduce the natriuretic effects of furosemide and thiazide in some patients. This effect was thought to be caused by inhibition of renal prostaglandin synthesis. During concomitant treatment with NSAIDs, the patient should be carefully monitored to determine the symptoms and diuretic efficacy of renal failure.

Lithium: NSAIDs caused an increase in plasma lithium levels and a decrease in renal lithium clearance. The mean minimum lithium concentration increased by 15% and renal clearance decreased by approximately 20%. This effect is thought to be caused by inhibition of renal prostaglandin synthesis by NSAIDs. Therefore, individuals should be carefully monitored for signs of lithium toxicity when NSAIDs are administered concurrently with lithium.

Methotrexate: NSAID drugs competitively inhibits methotrexate accumulation in rabbit kidney slices. This suggests that they may increase methotrexate toxicity. Caution should be exercised when concomitant use of NSAIDs with methotrexate.

Warfarin: Effects of warfarin and NSAIDs on gastrointestinal bleeding are synergistic; that is, the risk of serious gastrointestinal bleeding is higher in those who take both drugs together than those who take both drugs separately.

Cardiac glycosides: NSAIDs may exacerbate heart failure, reduce GFR, and increase plasma glycoside levels.

Ciclosporin: Cyclosporine-associated nephrotoxicity may be increased.

Phenylbutazone and probenecid: Phenylbutazone and probenecid may increase the risk of side effects of etodolac.

Anti-platelet agents (eg, warfarin, heparin) and selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine): May increase the risk of gastrointestinal bleeding.

Corticosteroids: They may increase the risk of gastrointestinal bleeding.

Tacrolimus: NSAIDs probably have increases the risk of nephrotoxicity when used with tacrolimus.

Zidovudine: NSAIDs increase the risk of hematological toxicity when used in combination with zidovudine.

Mifepristone: NSAIDs should be used 8-12 days after mifepristone, as their effectiveness may be reduced.

Quinolone antibiotics: In animal studies, the risk of convulsions is increased when NSAIDs are used with quinolone antibiotics. Therefore, the risk of convulsion is increased in NSAID and quinolone antibiotics.

Drug / laboratory test interactions

False-positive reactions to urinary bilirubin (urobilin) can be seen in the urine of patients receiving etodolac because of the phenolic metabolites of etodolac. The diagnostic 'dip-stick' method used to detect ketone bodies in urine has led to false-positive data in some patients receiving etodolac. In general, this phenomenon did not cause other clinically significant events and was not associated with dose.

Etodolac treatment caused a mild decrease in serum uric acid levels. In clinical studies, patients with arthritis who received etodolac treatment (600 mg-1000 mg / day) had an average decrease of 1-2 mg / dL after 4 weeks of treatment. These levels were then stable for treatment periods up to 1 year.

Additional information on special populations

No additional information on interactions in special populations.

Pediatric population: Safety and efficacy studies have not been conducted for etodolac in children under 18 years of age.

4.6 Pregnancy and lactation

General advice:

Pregnancy Category: First and second trimester C/Third trimester D

Severe gastrointestinal toxic effects such as unexpected bleeding, ulceration and perforation may occur in patients receiving chronic non-steroidal anti-inflammatory therapy. Use of etodolac should be discontinued immediately if gastrointestinal bleeding symptom is seen.

Women with childbearing potential / Contraception (Contraception)

Effective contraception during treatment is recommended for women with childbearing potential.

Pregnancy period

Animal studies are insufficient in terms of their effects on pregnancy and / or embryonal / fetal development and / or birth and / or postnatal development. The potential risk for humans is unknown. DOLARIT should not be used during pregnancy.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefit outweighs the potential risks to the fetus. NSAIDs should not be used during the last trimester of pregnancy because of the known effects of the fetus on the cardiovascular system in humans in terms of birth and closure of ductus arteriosus.

In studies with etodolac in rats, as with other drugs known to inhibit prostaglandin synthesis; dystocia, delayed labor and decreased number of living offspring. The effects of etodolac on birth in pregnant women are not known.

Lactation Period:

It is not known whether Etodolac passes into human milk. Since many drugs are transferred to human milk and etodolac has the potential for serious side effects in breastfed newborns, a decision should be made between breastfeeding or stopping the drug, considering the importance of the drug for the mother.

Reproductive ability / Fertility

Etodolac did not cause reproductive impairment in male and female rats up to 16 mg / kg (94 mg / m^2) oral doses. However, there was a decrease in the fertilized egg implantation in the 8 mg / kg group.

4.7 Effects on ability to drive and use machines

DOLARIT can cause dizziness, drowsiness, fatigue and visual disturbance (abnormal vision). Patients need to be aware of how they react to this medicine before driving or operating machines.

4.8 Undesirable effects

The reported undesirable effects are listed according to the following frequency rating.
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), unknown (can not be estimated from the given data).

Blood and lymph system diseases

Uncommon: Ecchymose, anemia, thrombocytopenia, increase in bleeding time, agranulocytosis, haemolytic anemia, leukopenia, neutropenia, pancytopenia.

Metabolism and nutritional diseases

Uncommon: edema, increase in serum creatinine, hyperglycaemia in a previously controlled diabetic patient, change in body weight, taste disorders

Nervous system diseases

Common: asthenia / fatigue, dizziness, depression, nervousness
Uncommon: Insomnia, somnolence, paresthesia, confusion

Eye diseases

Common: Blurred vision
Uncommon: photophobia, transient visual ddisorder, conjunctivitis

Ear and inner ear diseases

Common: Tinnitus

Uncommon: Deafness

Cardiac diseases

Uncommon: hypertension, congestive heart failure, facial flush, palpitations, syncope, vasculitis (including necrotizing and allergic), arrhythmia, myocardial infarction, cerebrovascular event

Respiratory, thoracic disorders and mediastinal disorders

Uncommon: asthma, pulmonary infiltration with eosinophilia, bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis

Gastrointestinal diseases

Common: Dyspepsia, abdominal pain, diarrhea, flatulence, nausea, constipation, gastritis, melena, vomiting

Uncommon: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, duodenitis, haemorrhagic or non-haemorrhagic peptic ulcer and / or perforation, intestine ulceration, pancreatitis, stricture or esophagitis with or without cardiospasm, colitis

Hepatobiliary diseases

Uncommon: Increase of liver enzymes, cholestatic hepatitis, hepatitis, cholestatic jaundice, jaundice, hepatic failure, liver necrosis

Skin and subcutaneous tissue diseases

Common: itching, rash

Uncommon: angioedema, sweating, urticaria, vesicobullous rash, cutaneous vasculitis with purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hyperpigmentation, alopecia, maculopapular rash, photosensitivity, skin peeling

Kidney and urinary tract diseases

Common: Dysuria, frequent urination

Uncommon: Increase of BUN, renal failure, renal disorder, renal papillary necrosis, cystitis, hematuria, renal calculi, interstitial nephritis, uterine bleeding irregularities

General disorders and treatment-related diseases

Common: Shivering and fever

Uncommon: Allergic reaction, anaphylactic / anaphylactoid reactions (including shock), infections, headache

4.9 Overdose and treatment

Symptoms

Following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care.

Gastrointestinal bleeding may occur and coma has occurred after overdose due to high levels of ibuprofen or mefenamic acid. Hypertension, acute renal failure, respiratory depression may also occur, but is very rare. Anaphylactoid reactions have been reported after therapeutic applications of NSAIDs and may occur after overdose.

Therapeutic measures

After overdose with a NSAID, patients should receive symptomatic and supportive treatment.

There is no specific antidote.

Intestinal decontamination may be indicated in patients with symptoms within 4 hours of ingestion or immediately after large doses (5-10 times the normal dose). This should be done via emesis and / or an osmotic cathartic with activated charcoal (60-100 g in adults, 1-2 g / kg in children). Since etodolac is highly protein bound, forced diuresis, urinary alkalinization, hemodialysis or hemoperfusion will probably not be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Classification: Antiinflammatory and antirheumatic agents (Non-steroids) – Acetic acid derivatives and related substances

ATC code: M01AB08

Etodolac is nonsteroidal antiinflammatory drug (NSAIDs) that show antiinflamatuar, analgesic and antipyretic effects in animal models. As with other NSAIDs, the mechanism of action of etodolac is

unclear, but is thought to be related to the inhibition of prostaglandin biosynthesis.
Etodolac is a racemic mixture of R (-) and S (+) etodolac. Like other NSAIDs, this drug has also been found to be active in the biological S (+) form in animals. Both enantiomers are stable and do not convert to the R (-) enantiomer S (+) enantiomer in vivo.
After a single dose of 200-400 mg of etodolac was given ½ hour after analgesia and maximum effect occurred within 1-2 hours. The analgesic effect lasted for 4-6 hours in general.

5.2 Pharmacokinetic properties

General properties

Pharmacokinetic properties do not differ in the elderly and young.
Etodolac's pharmacokinetics were evaluated in 267 normal subjects, 44 elderly patients (> 65 years), 19 patients with renal insufficiency (creatinine clearance 37-38 mL / min), 9 hemodialysis patients and 10 patients with compensated liver cirrhosis.
The kinetics of the etodolac applied by the oral route is best described by a two compartment model with first order absorption.
Pharmacokinetic interactions are not observed when etodolac is combined with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption:

Etodolac is well absorbed when taken orally. The relative bioavailability of the 200 mg capsule is 100% compared to the solution formulation. On the basis of mass balance studies, the systemic benefit of the etodolac from a tablet or capsule formulation is at least 80%. Etodolac does not undergo significant first-pass metabolism after oral administration. After a single dose of 200-600 mg, the mean peak plasma concentrations(± 1 SD) are approximately 14 ± 4 to 37 ± 9 μg / mL and this level is achieved within 80 ± 30 minutes. The relationship between AUC (area under the plasma concentration-time curve) and dose is linear up to a dose of 600 mg at 12 hours.
Peak concentrations of total and free etodolac of up to 400 mg doses per 12 hours are proportional to the applied dose, but the peak concentration reached after administration of the 600 mg dose is approximately 20% higher than anticipated based on lower doses.

Table 1 . Etodolac steady-state pharmacokinetic parameters (N=267)

Pharmacokinetic parameters	**Mean± SD**
Oral absorption amount (bioavailability) (F)	≥ % 80
Oral dose Clarence (CL/F)	47 ± 16 mL/hour/kg
Steady state volume (V_{ss}/F)	362 ± 129 mL/kg
Distribution half-life ($t_{1/2}/\alpha$)	0.71 ± 0.50 hour
Terminal half-life ($t_{1/2}/\beta$)	7.3 ± 4.0 hour

Etodolac absorption grade does not change when applied after eating. However, nutrient uptake decreases the peak concentration reached by about half and increases the time to peak concentration by 1.4-3.8 hours.

When etodolac is administered concurrently with an antacid, the degree of absorption is not affected. However, the peak plasma concentration reached is about 15-20% lower. There was no measurable effect on the time to peak.

Distribution:

Etodolac's steady state virtual plasma distribution volume is about 0.362 L / kg. Within therapeutic dose limits, etodolac binds to plasma proteins >99%. The free fraction is <1%, which is independent of the total etodolac concentration at the studied dose limits.

Protein binding - In vitro studies using peak serum concentrations in therapeutic doses reported in humans, the free fraction of etodolac has not been significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, pyroxicam, chlorpropamide, glipizide, gliburide, phenytoin and probenecid.

Biotransformation

Etodolac is metabolized intensively in the liver. The main pathway of etodolac and its metabolites is renal elimination. Plasma levels of etodolac obtained after the recommended doses are very different between individuals.

Elimination:

After oral dosing, mean plasma clearance of etodolac was 47 (± 16) mL / h / kg and terminal metabolism half-life was 7.3 (± 4.0) hours. Approximately 72% of the administered dose is found in urine as follows (expressed as a percentage of the administered dose):

- etodolac, unchanged 1%
- etodolac, glucuronide 13%

- hydroxylated metabolites (6-, 7- and 8-OH) 5%
- hydroxylated metabolite glucuronides 20%
- unspecified metabolites 33%

Elimination by faeces accounted for 16% of the dose.

Characteristics properties of patients

Elderly patients: In clinical trials etodolac clearance was found to be approximately 15% lower in elderly patients (> 65 years). In these studies, there was no age-related change in half-life or protein binding of etodolac and there was no change in expected drug accumulation. Based on the pharmacokinetic properties, dose adjustment is generally not needed in the elderly. However, depending on body size, dosage adjustment may be necessary in old age; because these patients may be more susceptible to antiprostaglandine effects than younger patients.

Renal insufficiency: No significant difference in total and free etodolac metabolism was observed in studies performed in patients with mild to moderate renal insufficiency (creatinine clearance 37-88 mL / min). In patients undergoing hemodialysis, there was a 50% increase in total etodolac clearance as the unbound fraction was 50% more, with no change in free etodolac clearance. This demonstrates the importance of protein binding in etodolac metabolism. Etodolac can not be removed from the body by dialysis.

Hepatic insufficiency: Total and free etodolac metabolism has not changed in patients with compensated liver cirrhosis. Although dose adjustment is not usually necessary in this patient group, etodolac clearance is dependent on liver function and the dose can be reduced in patients with severe hepatic insufficiency.

5.3 Preclinical safety data

Poisoning due to NSAIDs is primarily manifested by gastrointestinal disorders, hemorrhage and renal failure.

The pharmacological and toxicological properties of Etodolac are well known. Etodolac has no carcinogenic or mutagenic potential. It also has no embryogenic or teratogenic effects. However, in rats receiving 2-14 mg / kg / day, isolated changes in limb development occurred.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effect of etodolac was observed in mice and rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 18 months or 2 years, respectively. Etodolac was not mutagenic in in vitro tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an in vivo mouse micronucleus test.

However, the data obtained from the in vitro human peripheral lymphocyte test showed that etodolac-treated cultures (50 to 200 mcg / mL) had an increase in the gap number (3 to 5% of the unpainted region in the non-dislocated chromatids) compared to negative controls (2%); no difference was reported between controls and active groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

6. Pharmaceutical properties

6.1 List of excipients

Core tablet

- Microcrystalline cellulose
- Lactose monohydrate (obtained from cow's milk)
- Polyvinyl pyrrolidone K 30
- Sodium starch glycolate
- Colloidal silicon dioxide
- Magnesium stearate

Film coating*

- Polyvinyl alcohol
- Polythylene glycol 400
- Polythylene glycol 6000
- Tribasic calcium phosphate
- Talc

- Titanium dioxide

* *Provided as mixture.*

6.2 Incompatibilities

No incompatibilities have been reported with DOLARIT.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store in the original package and at room temperature below 25°C.

6.5 Property and contents of container

DOLARIT is supplied in 10 tablets of PVC / PVDC / Al blister packs and cardboard boxes.

6.6. Disposal of other medicinal products and other special precautions

Any unused product or waste material must be disposed of in accordance with the "Medical waste control regulation" and "Packaging and packaging waste control regulation".

7. Marketing authorisation holder

Drogsan İlaçları San. ve Tic. A.Ş.
Oğuzlar Mah. 1370. sok. 7/3
06520 Balgat-ANKARA
Tel: 0 312 287 74 10
Fax: 0 312 287 61 15

8. Marketing authorisation number(s)

2016/229

9. Date of first authorisation/renewal of the authorization

Date of first authorisation	18.05.2016
Renewal of the authorization	-

10. Date of revision of the text

24/06/2021