SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Dolarit 400 mg Film Tablet

2. Qualitative and quantitative composition

Active ingredient: Each film-coated tablet contains 400 mg Etodolac.

Excipients: Each film-coated tablet contains 275 mg of lactose monohydrate (obtained from cow's milk.), 9 mg of sodium starch glycolate.

For the excipients: see section 6.1.

3. Pharmaceutical form

Film coated tablet.

White, oval, film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

It is indicated for the treatment of signs and symptoms 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/administration frequency and duration:

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

The adult dose, 400 mg/day, can be taken in two divided doses or as a single dose.

Route of administration

For oral administration. To be taken preferably with or after food.

Additional information on special populations:

Kidney failure:

Studies in patients with mild and moderate renal impairment (creatinine clearance 37-38 mL/min) did not show significant differences in total and free etodolac metabolism. Since the unbound fraction was 50% greater in patients undergoing hemodialysis, a 50% increase in total etodolac clearance was observed, while free etodolac clearance remained unchanged. This indicates the importance of protein binding in etodolac metabolism. Etodolac cannot be removed from the body by dialysis. It should not be used in severe renal failure.

Liver failure:

Total and free etodolac metabolism was not altered in patients with compensated liver cirrhosis. Although dose adjustment is generally not required in this patient group, the clearance of etodolac is dependent on liver function and should not be used in patients with severe hepatic impairment.

Pediatric Population:

Etodolac has not been evaluated in pediatric patients for efficacy and safety, so it is not recommended for use in children.

Geriatric Population:

No dosage adjustment is required in elderly patients.

Elderly patients are at increased risk of adverse reactions.

Undesirable effects can be minimized by using the lowest effective dose for the shortest time necessary to control symptoms. Patients should be closely monitored for the risk of gastrointestinal bleeding during NSAID therapy.

4.3 Contraindications

DOLARIT is contraindicated in patients with known hypersensitivity to etodolac or any ingredient in the tablet.

Due to possible cross-drug reactions, DOLARIT should not be used in patients who develop allergic reactions during treatment with aspirin or other non-steroidal anti-inflammatory drugs, 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 previous treatment with NSAIDs.
DOLARIT should not be used in patients with severe heart failure, immediately before or after bypass and heart surgery.
Etodolac is also contraindicated in patients with active peptic ulcer or a history of peptic ulcer disease (including gastrointestinal haemorrhage caused by other non-steroidal anti-inflammatory drugs).
It is contraindicated in the last trimester of pregnancy.
It is contraindicated in severe hepatic and renal failure.

4.4 Special warnings and precautions for use

Cardiovascular (CV) risk
• NSAIDs may increase the risk of potentially fatal CV thrombotic events, myocardial infarction and stroke. This risk may increase depending on the duration of use. The risk may be higher in patients with CV disease or those with CV disease risk factors.

DOLARIT is contraindicated in the treatment of pain before coronary artery bypass surgery.

Gastrointestinal (GI) risks
NSAIDs cause serious GI adverse effects such as bleeding, ulceration, gastric or intestinal perforation, which can be fatal. These adverse events can occur at any time, with or without a forewarning symptom.

Elderly patients are at higher risk for serious GI effects.

Warnings:

Cardiovascular thrombotic effects:
In clinical studies with many COX-2 selective and non-selective non-steroidal anti-inflammatory (NSAID) drugs for up to 3 years, the risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal, is high. A similar risk can be found with all COX-2

selective and non-COX-2 selective NSAIDs. The risk may be higher in patients with known cardiovascular disease or with risk factors for cardiovascular disease. In patients treated with NSAIDs, the lowest effective dose should be used for the shortest possible duration to minimize the potential risk of adverse cardiovascular effects. Even if cardiovascular symptoms have not been seen before, patients and physicians should be alert to the occurrence of such events. Patients should be counseled about the signs and/or symptoms of serious cardiovascular events and what to do if they occur.

There is no consistent evidence that concomitant aspirin reduces the risk of serious cardiovascular thrombotic events, which is increased by the use of NSAIDs. Concomitant use of aspirin and an NSAID increases the risk of serious gastrointestinal effects (see Gastrointestinal effects).

An increased incidence of myocardial infraction and stroke was observed in two large, controlled clinical trials using COX-2 selective NSAIDs for pain management within the first 10-14 days after coronary artery bypass surgery (see Contraindications).

Hypertension:

Like other NSAIDs, DOLARIT can lead to the onset of hypertension or worsening of pre-existing hypertension, which may increase the incidence of cardiovascular events. When patients using thiazide or loop diuretics take NSAIDs, their response 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 start of NSAID therapy and throughout therapy.

Congestive heart failure and edema:

Fluid retention and edema have been observed in some patients using 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 time of the treatment and without any warning symptoms; may cause serious gastrointestinal adverse effects in the form of inflammation, bleeding, ulceration or perforation of the stomach, small intestine or large intestine, which can result in death. Only one in five patients with severe upper

gastrointestinal complaints using NSAIDs is symptomatic. It has been shown that severe upper gastrointestinal tract ulcers, major bleedings or perforations associated with NSAID drug use occur in approximately 1% of patients treated for 3-6 months, and in 2-4% of patients treated for one year. These trends continue with longer duration of use and the likelihood of serious gastrointestinal adverse events increases during the treatment cycle. However, even with short-term treatment, there is a risk.

NSAIDs should be used with extreme 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 are more than 10 times more likely to develop gastrointestinal bleeding than patients without any of these risk factors. In patients administered NSAIDs; Concurrent use of oral corticosteroids or anticoagulants, long-term use of NSAIDs, smoking habits, alcohol use, advanced age and poor general health are other factors that increase the risk of gastrointestinal bleeding. The majority of spontaneous fatal gastrointestinal events occur in patients who are elderly or in poor general health; therefore, particular care should be taken in the treatment of this population.

To minimize the potential risk of gastrointestinal adverse effects in patients treated with NSAIDs, the lowest effective dose should be administered for the shortest possible duration. During NSAID therapy, patients and physicians should be alert for signs and symptoms of gastrointestinal ulceration and bleeding, and prompt further evaluation and treatment should be initiated if serious gastrointestinal adverse effects are suspected. This should include discontinuing NSAID therapy until the serious gastrointestinal adverse effect resolves. Alternative treatments 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 whom renal prostaglandins play a compensatory role in providing perfusion of the kidney. Administration of an NSAID to these patients may result in a dose-dependent decrease in prostaglandin production and renal blood flow to such an extent that it results in marked renal decompensation. Patients at such risk; patients with renal dysfunction, heart failure, liver dysfunction, those using diuretics and ACE inhibitors, and the elderly. With the discontinuation of NSAID therapy, the pre-treatment state is usually restored.

Advanced Renal Disease

No information is available on the use of DOLARIT in patients with advanced renal disease in controlled clinical studies. Therefore, treatment with DOLARIT is not recommended in patients with advanced renal disease. If DOLARIT therapy needs to be initiated, close monitoring of the patient's renal function is recommended.

Anaphylactoid Reactions:

As with other NSAIDs, anaphylactoid reactions may occur in patients who have not previously used etodolac. Etodolac; It should not be given to patients with the aspirin triad (asthma, urticaria, or similar allergic reactions to aspirin or other NSAIDs).

Serious, potentially fatal bronchospasm may occur with the ingestion of aspirin or other NSAIDs, predominantly in patients with bronchial asthma, vasomotor rhinitis, and nasal polyposis. 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

All 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 can occur without any symptoms. Patients should be informed of the signs and symptoms of serious skin reactions and should be told that the drug should be discontinued at the appearance of a skin rash or any other sign of hypersensitivity.

Pregnancy

Etodolac is not recommended for use in the late stages of pregnancy, as it may cause premature closure of the ductus arteriosus.

Each film tablet contains 275 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions

General:

Etodolac should not be used in place of corticosteroids or in the absence of corticosteroid therapy. Sudden discontinuation of corticosteroids may lead to exacerbation of the disease. In patients on long-term corticosteroid therapy, if a decision is made to discontinue corticosteroid therapy, maintenance should be tapered off.

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

Hepatic Effects:

Borderline elevations of one or more liver function tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT and AST (approximately three times the upper limit of normal or more) in approximately 1% of patients treated with NSAIDs in clinical trials.) have been reported. These changes in laboratory findings may progress, remain unchanged, or may be transient despite continued therapy. Serious hepatic reactions such as jaundice and fatal fulminant hepatitis, hepatic necrosis and hepatic failure (some with fatal outcome) have been reported rarely with the use of NSAIDs.

Patients with symptoms and/or signs of liver dysfunction or abnormal liver tests while on etodolac therapy should be evaluated for evidence of a more severe hepatic reaction occurring. Etodolac treatment should be discontinued if clinical signs and symptoms consistent with liver disease occur or if systemic manifestations occur (such as rash, eosinophilia).

Hematological Effects:

Anemia is sometimes seen in patients taking Etodolka or other NSAIDs. This is because; There may be fluid retention, occult or extensive gastrointestinal blood loss, or an incompletely defined effect on erythropoiesis. Patients on long-term use of NSAIDs, including etodolac, should have their hemoglobin or hematocrit measured if any signs or symptoms of anemia are observed.

NSAIDs inhibit platelet aggregation and these agents have been shown to prolong bleeding time in some patients. Unlike aspirin, its effects on platelet function are quantitatively less, of shorter duration, and reversible. Patients treated with etodolac and who have adverse effects of changes

in platelet function (such as patients with coagulation disorders or those on 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 causes severe bronchospasm, which can be fatal. Etodolac should not be used in such patients, as cross-reactivity, including bronchospasm, has been reported between aspirin and other NSAIDs, and caution should be exercised in patients with known pre-existing 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 and even death. Although serious cardiovascular events can occur without warning symptoms, patients should look out for signs and symptoms such as chest pain, shortness of breath, weakness, slurred speech, and seek medical attention if they experience any similar 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 ulceration and bleeding, which may require hospitalization and even be fatal. Because severe gastrointestinal ulceration and bleeding can occur without warning symptoms, physicians should caution patients on chronic therapy to watch for signs and symptoms of ulceration and bleeding and should be monitored for any signs or symptoms including epigastric pain, dyspepsia, melena and hematemesis should also inform the importance of this monitoring (See Warnings-Gastrointestinal effects-Risk of ulceration, bleeding and perforation).
Etodolac, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis that require hospitalization and can even be fatal. Although serious skin reactions can occur without warning, patients should look out for other signs and symptoms of hypersensitivity such as skin rash and blisters, fever or itching and seek medical attention if they notice any signs or symptoms. If any type of rash occurs, patients should be instructed to stop the medication immediately and consult their physician as soon as possible.

Patients should be instructed to report any signs and symptoms of unexplained weight gain or edema to their physician immediately.
Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and flu-like syndrome). If these occur, patients should be instructed to stop treatment and seek medical attention immediately.
Patients should also be instructed to seek emergency 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 last stages of pregnancy; because it will cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious gastrointestinal ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of gastrointestinal bleeding. As with other NSAIDs, patients on long-term etodolac therapy should have their complete blood count and chemical profile checked periodically for signs and symptoms of anemia.
Etodolac should be discontinued if clinical signs and symptoms of liver disease occur or if systemic manifestations (such as eosinophilia, rash) occur 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.

4.5 Interaction with other medicinal products and other forms of interaction

ACE-inhibitors: Studies have shown that NSAIDs can reduce the antihypertensive effects of ACE-inhibitors. This interaction should be considered in patients receiving concomitant NSAIDs and ACE-inhibitors.
Aspirin: When etodolac is co-administered with aspirin, its protein binding is reduced, but the clearance of free etodolac is not changed. The clinical significance of this interaction is unknown. However, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended due to the potential for increased side effects.

Furosemide: In clinical studies and post-marketing observations, etodolac has been shown to reduce the natriuretic effects of furosemide and thiazides 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 for signs of renal impairment and diuretic efficacy.

Lithium: NSAIDs have produced 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 concomitantly with lithium.

Methotrexate: NSAIDs have been noted to competitively inhibit methotrexate accumulation in rabbit kidney slices. This suggests that they may increase methotrexate toxicity. Caution should be exercised when NSAIDs are used simultaneously with methotrexate.

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

Cardiac glycosides: NSAIDs can exacerbate heart failure, decrease GFR, and increase plasma glycoside levels.

Cyclosporines: Cyclosporine-associated nephrotoxicity may be increased.

Phenylbutazone and probenecid: Phenylbutazone and probenecid may increase the risk of side effects from 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 are likely to increase the risk of nephrotoxicity when used with tacrolimus.

Zidovudine: NSAIDs increase the risk of haematological toxicity when used with zidovudine.

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

Quinolone antibiotics: In animal studies, it was determined that the risk of convulsions increases when NSAIDs are used together with quinolone antibiotics. Therefore, concomitant use of NSAIDs and quinolone antibiotics has an increased risk of convulsions.

Drug/lab test interactions

Since phenolic metabolites of etodolac are present in the urine of patients administered etodolac, a false positive reaction for urinary bilirubin (urobilin) may occur. The diagnostic dip-stick method used to detect ketone bodies in the urine has resulted in false-positive data in some patients treated with etodolac. In general, this phenomenon did not cause other clinically significant events and was not dose related.

Etodolac treatment resulted in a slight decrease in serum uric acid levels. In patients with arthritis treated with etodolac (600 mg-1000 mg/day) in clinical studies, mean reductions of 1-2 mg/dL were seen after 4 weeks of treatment. Thereafter, these levels remained stable for up to 1 year of treatment.

Additional Information for Special Populations

Geriatric population: In clinical studies for the safety and efficacy of the drug, no difference was observed between the elderly and young groups. In pharmacokinetic studies, there was no age-related difference in Etodolac half-life and protein binding, and there was no change in expected drug accumulation. Therefore, there is no need for dose adjustment in the elderly.

Pediatric population: Since safety and efficacy studies have not been conducted for etodolac in children under 18 years of age, this drug is not recommended for use in children.

4.6 Pregnancy and lactation

General advice:

Pregnancy Category is C (D in the 3rd trimester of pregnancy).

Serious gastrointestinal toxic effects such as unexpected bleeding, ulceration and perforation may occur in patients receiving chronic non-steroidal anti-inflammatory therapy. Etodolac should be discontinued immediately when signs of gastrointestinal bleeding appear.

Women with childbearing potential / Contraception (Contraception)

Effective contraception is recommended during treatment in women of childbearing potential.

Pregnancy period

Animal studies are inconclusive regarding effects on pregnancy and/or embryonal/foetal development and/or parturition 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 risk to the foetus. NSAIDs should not be used in the last trimester of pregnancy because of the known effects on the cardiovascular system of the fetus in humans in terms of delivery and closure of the ductus arteriosus.

In studies with etodolac in rats, as with other drugs known to inhibit prostaglandin synthesis; dystocia, delayed birth, and a decrease in the number of surviving puppies. The effects of Etodolac on childbirth in pregnant women are unknown.

Lactation Period:

It is not known whether Etodolac is excreted in human milk. Because many drugs are excreted in human milk and etodolac has the potential for serious adverse effects in breastfed newborns, a

decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Reproductive ability / Fertility

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

4.7 Effects on ability to drive and use machines

Etodolac can cause dizziness, lightheadedness, tiredness, and vision abnormalities. Patients should be warned to be alert to the effects of this drug before driving or using machinery.

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 predicted from the given data).

Blood and lymphatic system diseases

Uncommon: Ecchymosis, anaemia, thrombocytopenia, increased bleeding time, agranulocytosis, haemolytic anaemia, leukopenia, neutropenia, pancytopenia.

Metabolism and nutritional diseases

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

Nervous system diseases

Common: Asthenia/fatigue, dizziness, depression, nervousness
Uncommon: insomnia, somnolence, paresthesia, confusion

Eye diseases

Common: blurred vision

Uncommon: Photophobia, transient visual impairment, conjunctivitis

Ear and inner ear diseases

Common: tinnitus

Uncommon: Deafness

Cardiac diseases

Uncommon: Hypertension, congestive heart failure, flushing, palpitation, syncope, vasculitis (including necrotizing and allergic), arrhythmias, myocardial infraction, cerebrovascular accident

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal diseases

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

Uncommon: thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, duodenitis, peptic ulcer and/or perforation with or without bleeding, bowel ulceration, pancreatitis, esophagitis with or without stricture or cardiospasm, colitis

Hepatobiliary diseases

Uncommon: Liver enzyme elevation, cholestatic hepatitis, hepatitis, cholestatic jaundice, jaundice, hepatic failure, hepatic necrosis

Skin and subcutaneous tissue diseases

Common: Pruritus, rash

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

Kidney and urinary tract diseases

Common: Dysuria, frequent urination

Uncommon: BUN increased, renal failure, renal impairment, renal papillary necrosis, cystitis, haematuria, renal calculus, interstitial nephritis, uterine bleeding irregularities.

General disorders and administration site conditions

Common: chills and fever

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

4.9 Overdose its treatment

Symptoms

Symptoms after NSAID drug overdose are usually limited to lethargy, somnolence, nausea, vomiting, and epigastric pain and usually resolve with supportive treatment.

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

Therapeutic measures

After overdose with an NSAID, patients should receive symptomatic and supportive treatment. There is no specific antidote.

Bowel decontamination may be indicated in patients with symptoms within 4 hours of ingestion, or immediately after large overdoses (5-10 times the normal dose). This should be done by means of activated charcoal (60-100 g in adults, 1-2 g/kg in children) with emesis and/or an osmotic cathartic.

Because etodolac is highly protein bound, forced diuresis, urine alkalinization, hemodialysis, or hemoperfusion will likely not be beneficial.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products (Non-steroidal) - Acetic acid derivatives and analogues

ATC code: M01AB08

Etodolac is a nonsteroidal anti-inflammatory (NSAID) drug that has anti-inflammatory, analgesic, and antipyretic effects in animal models. As with other NSAIDs, the exact mechanism of action of etodolac is unknown, but is thought to be related to inhibition of prostaglandin biosynthesis.

Etodolac is a racemic mixture of R (-) and S (+) etodolac. Like other NSAIDs, the S (+) form of this drug has been found to be biologically active in animals. Both enantiomers are stable and the R (-) enantiomer does not convert to the S (+) enantiomer in vivo.

Analgesia was achieved ½ hour after administration of a single dose of 200-400 mg of etodolac, with the maximum effect occurring within 1-2 hours. The analgesic effect generally persisted for 4-6 hours.

5.2 Pharmacokinetic properties

General features

The pharmacokinetics of etodolac were evaluated in 267 normal subjects, 44 elderly patients (> 65 years), 19 patients with renal impairment (creatinine clearance 37-38 mL/min), 9 patients on hemodialysis, and 10 patients with compensated liver cirrhosis.

The kinetics of orally administered etodolac are best described by the two-compartment model with first-order absorption.

No pharmacokinetic interaction is observed when etodolac is administered concomitantly with phenytoin, glyburide, furosemide or hydrochlorothiazide.

<u>Absorbation:</u>

Etodolac is well absorbed and the relative bioavailability of the 200 mg capsule is 100% compared to the solution formulation. Based on mass balance studies, the systemic efficacy of etodolac from the tablet or capsule formulation is at least 80%. Etodolac does not undergo significant first pass metabolism after oral administration. Mean (± 1 SD) peak plasma

concentrations range from approximately 14 ± 4 to 37 ± 9 µg/mL after a single dose of 200-600 mg and are reached within 80 ± 30 minutes. For doses up to 600 mg every 12 hours, the relationship between AUC (area under the plasma concentration-time curve) and dose is linear. Peak concentrations of total and free etodolac up to doses of 400 mg every 12 hours are proportional to the dose administered, but the peak concentration after administration of the 600 mg dose is approximately 20% higher than would be predicted 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

The degree of absorption does not change when etodolac is administered after a meal. However, food intake decreases the peak concentration reached by about half and increases the time to peak concentration by 1.4-3.8 hours.

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

Distribution:

The steady-state virtual plasma volume of distribution of etodolac is approximately 0.362 L/kg. Etodolac is >99% bound to plasma proteins within the therapeutic dose range. The free fraction is < 1%, which is independent of the total etodolac concentration at the dose limits investigated. Protein binding – Data from in vitro studies using peak serum concentrations at reported therapeutic doses in humans showed that the free fraction of etodolac was not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Biotransformation:

Etodolac is extensively metabolized in the liver. The main route of elimination of etodolac and its metabolites is renal elimination. Etodolac plasma levels achieved after recommended doses vary widely between individuals.

Elimination:

The mean plasma clearance of etodolac after oral dosing is 47 (± 16) mL/hr/kg and the terminal metabolic half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is found in the urine as follows (indicated 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%

Fecal excreta produced 16% of the dose.

Characteristics features of patients

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

Renal Impairment: Studies in patients with mild to moderate renal impairment (creatinine clearance 37-38 mL/min) did not show significant differences in total and free etodolac metabolism. Since the unbound fraction was 50% greater in patients undergoing hemodialysis, a 50% increase in total etodolac clearance was observed, while free etodolac clearance remained unchanged. This indicates the importance of protein binding in etodolac metabolism. Etodolac cannot be removed from the body by dialysis.

Hepatic impairment: Total and free metabolism of etodolac was not altered in patients with compensated liver cirrhosis. Although dose adjustment is generally not required in this patient group, the clearance of etodolac is dependent on hepatic function and the dose may be reduced in patients with severe hepatic impairment.

5.3 Preclinical safety data

Intoxication due to NSAIDs is manifested primarily by gastrointestinal disorders and hemorrhage, and kidney disorders.

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

Carcinogenesis, Mutagenesis and Reproductive Disorders

Etodolac was not carcinogenic when administered to mice at oral doses of 15 mg/kg/day (45 and 89 mg/m², respectively) or less for 2 years and rats for 18 months. Etodolac was not mutagenic in in vitro tests with S. typhimurium and mouse lymphoma cells and in an in vivo mouse micronucleus test. However, according to data from the in vitro human peripheral lymphocyte assay, there was an increase in the number of gaps (unstained area 3.0 - 5.3% in non-dislocation chromatids) in etodolac-treated cultures (50 - 200 mcg/mL) compared to negative controls (2.0%); No other difference was reported between controls and active drug administered groups. Etodolac did not cause reproductive harm in male and female rats at oral doses up to 16 mg/kg (94 mg/m2). However, there was a decrease in fertilized egg implantation in the 8 mg/kg group.

6. Pharmaceutical particulars

6.1 List of excipients

Core tablet

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

Film coating*

- Polyvinyl alcohol
- Polythylene glycol
- Tribasic calcium phosphate
- Talc
- Titanium dioxide

** Provided as mixture.*

6.2 Incompatibilities

No incompatibilities have been reported.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

DOLARIT film tablet is distributed in PVC/PVDC-Aluminum blister, packed in carton boxes.

Dose units: 14 or 28 film tablets

6.6 Special precautions for disposal and other handling

None

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)

223/83 (in Turkey)

9. Date of first authorisation/renewal of the authorization (in Turkey)

Date of first authorisation	08.03.2010
Renewal of the authorization	11.08.2015

10. Date of revision of the text

30/05/2015