SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODOL®film-coated tablets 200 mg

PRODOL®film-coated tablets 400 mg

etodolac

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Etodolac 300 mg.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Etodolac is indicated for acute or long term use in :

i) Osteoarthritis

ii) Rheumatoid arthritis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral administration

To be taken preferably with or after food.

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

Usual adult dose1 -2 film-coated tablets daily in two divided doses or as a single daily dose.

Children: It is not recommended for use in children.

Elderly: No dosage adjustment in initial dosage is generally required in the elderly (see precautions).

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID I considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

4.3 CONTRAINDICATIONS

Etodolac is contraindicated in patients who have a previous history of hypersensitivity to etodolac or to any of the excipients.

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Etodolac should not be used in patients with severe heart failure, hepatic failure and renal failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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).

The use of Etodolac with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided (see section 4.5).

Respiratory disorders:

Caution is required if etodolac is administered to patients suffering from, or with a previous history of bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. The dose should be low and renal function should be monitored in these patients (see also section 4.3).

Etodolac should be used with caution in patients with fluid retention, hypertension or heart failure.

Hepatic and renal function, haematological parameters of patients on long term use of etodolac should be regularly reviewed.

Platelets

Although non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets as does aspirin, all such drugs which inhibit the biosynthesis of prostaglandins may interfere with platelet function.

Patients who may be adversely affected due to inhibition of platelet function should be carefully observed.

Elderly

No dosage adjustment is generally necessary in the elderly. However, caution should be exercised in treating the elderly, and when individualising their dosage, extra care should be taken while increasing the dose. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Paediatrics

Safety and efficacy in children have not been established and therefore etodolac is not recommended in children.

Cardiovascular and cerebrovascular effects:

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 NSAID 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 Etodolac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Etodolac after careful consideration.

Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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

When GI bleeding or ulceration occurs in patients receiving Etodolac, the treatment should be withdrawn.

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

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Dermatological:

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 for 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. Etodolac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility:

The use of Etodolac 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 Etodolac should be considered.

This product contains lactose. Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Since etodolac is extensively protein-bound, it may be necessary to modify the dosage of other highly protein - bound drugs.

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Lithium: Decreased elimination of lithium

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Nephrotoxicity associated with cyclosporine may be enhanced.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Prothrombin time may be prolonged when etodolac and other NSAIDs are given along with warfarin thus leading to increased risk of bleeding.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Laboratory test: Bilirubin tests can give a false positive result due to the presence of phenolic metabolites of etodolac in the urine.

4.6 PREGNANCY AND LACTATION

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. Safety of etodolac during lactation has not been established. Use of etodolac should if possible, be avoided when breastfeeding

Fertility

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Etodolac 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. If affected, patients should not drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

The most commonly-observed adverse events are gastrointestinal in nature.

Blood and lymphatic system disorders

Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Immune system disorders

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis, anaphylactoid reaction

(b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

Nervous System disorders

Depression, headaches, dizziness, insomnia, confusion, hallucinations, disorientation (See section 4.4) paraesthesia, tremor, weakness, nervousness and drowsiness, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting.

Eye disorders

Visual disturbances (abnormal vision), optic neuritis

Ear and labyrinth disorders

Tinnitus, vertigo

Cardiac disorders

Oedema, hypertension, palpitation and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Vascular disorders

Vasculitis

Gastrointestinal disorders

Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4).

Nausea, vomiting, diarrhoea, dyspepsia, epigastric pain, ulcerative stomatitis, abdominal pain, constipation, flatulence, haematemesis, melaena, gastrointestinal ulceration, indigestion, heartburn, rectal bleeding. Exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hepato-biliary disorders:

Abnormal liver function (bilirubinuria) hepatitis and jaundice.

Skin and subcutaneous tissue disorders:

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

Renal and urinary disorders

Dysuria, urinary frequency (<1%), nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

General disorders

Malaise, fatigue, asthenia, chills, fever

4.9 OVERDOSE

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionall convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured. Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic Classification

M01a B (Anti-Inflammatory and Anti-Rheumatic Agents)

Mode Of Action

Etodolac is a non steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic actions. The mode of action is thought to be through inhibition of the cyclo-oxygenase enzyme involved in prostaglandin synthesis.

Inhibition of prostaglandin synthesis and COX-2 selectivity: All non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the formation of prostaglandins. It is this action which is responsible both for their therapeutic effects and some of their side-effects. The inhibition of prostaglandin synthesis observed with etodolac differs from that of other NSAIDs. In an animal model at an established anti-inflammatory dose, cytoprotective PGE concentration in the gastric mucosa have been shown to be reduced to a lesser degree and for a shorter period than other NSAIDs. This finding is consistent with subsequent in-vitro studies which have found etodolac to be selective for induced cyclo-oxygenase 2 (COX-2, associated with inflammation) over COX-1 (cytoprotective).

Furthermore, studies in human cell models have confirmed that etodolac is selective for the inhibition of COX-2.

The clinical benefit of preferential COX-2 inhibition over COX-1 has yet to be proven.

Anti-inflammatory effects: Experiments have shown etodolac to have marked anti-inflammatory activity, being more potent than several clinically established NSAIDs.

5.2 PHARMACOKINETIC PROPERTIES

Etodolac is well absorbed when taken orally. Following oral administration of 200 mg or 300mg of etodolac, the peak plasma concentration of 10-18 µg/ml and 36 µg/ml respectively is achieved in about 1-2 hours. Etodolac plasma concentrations, after multiple dose administration within therapeutic range, are only slightly higher than after single dose. Etodolac may be given with food or coadministered with antacids, as the extent of absorption of etodolac is not affected when administered after a meal or with an antacid. Etodolac is more than 99% bound to plasma proteins.

Etodolac penetrates readily into synovial fluid following oral administration in patients with arthritis. Consistent with the lower levels of total protein and albumin in synovial fluid compared to serum, the synovial fluid free etodolac auc (0-24 h) is 72% higher than the value for serum. In the post-distributive phase, total and free etodolac concentration in synovial fluid consistently exceeds those in serum, with mean synovial fluid: serum ratios of 1.18 and 3.25, between 8 and 32 hours post dose respectively.

Etodolac is extensively metabolised in the liver. Approximately 72% of the administered dose is recovered in the urine as inactive metabolites. 16% of the dose is excreted through faeces. The plasma half life of etodolac is 6-7.4 hours.

Studies in the elderly have shown similar pharmacokinetics as in younger individuals. No dosage adjustment is needed in the elderly. Since etodolac clearance is dependent on hepatic function, patients with severe hepatic failure may have reduced clearance. No change in pharmacokinetics has been noticed in patients of mild to moderate renal impairment compared to normals. In usual therapeutic doses etodolac decreases serum uric acid levels by 1-2 mg % after four weeks of administration.

5.3 PRECLINICAL SAFETY DATA

The pharmacological and toxicological properties of etodolac are well established. Etodolac has no carcinogenic or mutagenic potential. It has shown no embryogenic or teratogenic effects. However an isolated alteration of limb development has occurred in rats receiving 2-14mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate, microcrystalline cellulose, povidone, copovidone, sodium starch glycollate, magnesium stearate and silicon dioxide, colloidal.

6.2 Incompatibilities

No incompatibilities have been reported with etodolac.

6.3 Shelf life

2 Years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

30 (3×10) film-coated tablets of 200 mg etodolac in PVC/PVDC blister in carton box.

30 (3×10) film-coated tablets of 400 mg etodolac in PVC/PVDC blister in carton box.

6.6 Special precautions for disposal and other handling

None.

7. Marketing and manufacturer authorisation holder

ZADA Pharmaceuticals d.o.o.

Donji Bistarac without number

75300 Lukavac

Bosnia and Herzegovina.