SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MAXIMUS 100 mg Film Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of flurbiprofen.

Excipient(s):

Lactose Monohydrate (Tablettose) 26.00 mg

See 6.1 for all excipients.

3. PHARMACEUTICAL FORM

Film tablet.

Pink color film tablet.

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 and dysmenorrhea.

4.2 Posology and method of administration

Posology/Application frequency and duration:

As with other nonsteroidal anti-inflammatory drugs (NSAIDs), the lowest dose should be given to each patient to minimize undesirable effects. Therefore, initial therapy with MAXIMUS should be observed and the dose and frequency adjusted to suit the needs of each individual patient.

The recommended daily dose is 150-200 mg in divided doses.

Depending on the severity of the symptoms, the daily dose can be increased to a total of 300 mg.

The recommended dose of MAXIMUS for the relief of signs and symptoms of rheumatoid arthritis or osteoarthritis is 200 to 300 mg per day to be administered in two, three or four divided doses per day.
In menstrual cramps, it is 100 mg at the onset of symptoms, followed by 50-100 mg every 4-6 hours. The maximum daily dose is 300 mg.
The highest recommended single dose for multiple dose administration is 100 mg.
It should be taken immediately after meals, with a sufficient amount of liquid (a glass of water).

Additional information on special populations:

Kidney failure:

In patients with significantly reduced renal function, dose reduction may be required to prevent accumulation of flurbiprofen metabolites. Such patients should be closely monitored (see Special warnings and precautions for use - Renal effects). It should not be used in patients with severe renal impairment (see Contraindications).

Liver failure:

A patient with signs and/or symptoms indicative of hepatic impairment or with abnormal liver test values should be evaluated for the development of a more severe hepatic reaction during treatment with MAXIMUS (see Special warnings and precautions for use - Hepatic effects). It should not be used in patients with severe hepatic impairment (see Contraindications).

Pediatric population:

No data are available on its use in children.

Geriatric population:

It should be used with caution in patients over 65 years of age. As with other NSAIDs, gastrointestinal complications such as ulcers, bleeding, flatulence and abdominal pain are more common in elderly patients than younger patients.

4.3 Contraindications

MAXIMUS is contraindicated in patients with known hypersensitivity to flurbiprofen. MAXIMUS should not be used in patients with asthma, urticaria, or who have had allergic-type reactions following the use of aspirin or any other NSAID. Severe, rarely fatal,

anaphylactic-like reactions to NSAIDs have been reported in such patients (see Special warnings and precautions for use - Anaphylactoid reactions and pre-existing asthma). MAXIMUS should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps or severe, potentially fatal bronchospasm after taking aspirin or NSAIDs.

The use of flurbiprofen is contraindicated in patients with active or previous peptic ulcer.

It is contraindicated in patients with a history of gastrointestinal bleeding or perforation associated with previous NSAID therapy.

Contraindicated in gastrointestinal bleeding, cerebrovascular bleeding and other bleeding.

It is contraindicated in patients with severe heart failure, hepatic failure and renal failure.

It is contraindicated to use as a preoperative pain reliever in patients who have undergone coronary artery by-pass graft operation.

Contraindicated in the last trimester of pregnancy.

4.4 Special warnings and special precautions for use

Concomitant use of MAXIMUS with other systemic NSAIDs other than aspirin, including COX-2 inhibitors, should be avoided. Concomitant use of systemic NSAIDs and other NSAIDs may increase the frequency of gastrointestinal (GI) ulcers and bleeding.

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.
- It is contraindicated to use MAXIMUS as a pre- and postoperative pain reliever in patients who have undergone coronary artery by-pass graft operation.

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 (CV) thrombotic effects:

Up to 3 years of clinical studies with some selective COX-2 inhibitors or non-selective NSAIDs have shown that they can lead to an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. Patients with known cardiovascular disease may be at greater risk. To minimize the risk of cardiovascular adverse events in patients treated with MAXIMUS, the lowest effective dose should be used for the shortest possible duration. Even if cardiovascular symptoms have not been experienced before, physicians and patients should be alert to the occurrence of such events. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and what to do if they occur (see section 4.3 Contraindications).

There is no consistent evidence to suggest that concomitant use of aspirin reduces the increased risk of serious CV thrombotic events associated with NSAID use. Concomitant use of aspirin and MAXIMUS increases the risk of serious gastrointestinal events (see section 4.4 Special warnings and precautions for use, Gastrointestinal (GI) effects – risk of GI ulceration, bleeding and perforation)

Based on the results of two large controlled clinical trials, it was observed that the use of a COX-2 selective NSAID for pain management between 10 and 14 days following coronary artery bypass grafting resulted in an increased risk of myocardial infarction and stroke (see section 4.3 Contraindications).

Hypertension:

As with all other NSAIDs, flurbiprofen can lead to the development of hypertension or worsening of pre-existing hypertension, both of which increase the risk of cardiovascular events. The use of NSAIDs in patients taking thiazides or loop diuretics may result in impaired response to these treatments. NSAIDs, including flurbiprofen, should be used with caution in patients with hypertension. Blood pressure should be closely monitored at the start of flurbiprofen therapy and throughout the course of therapy.

Congestive heart failure and edema:

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs, including MAXIMUS. Therefore, MAXIMUS should be used with caution in patients with fluid retention, hypertension or heart failure.

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

Serious GI toxicity, which can be fatal, such as inflammation, bleeding, ulceration, or perforation of the stomach, small intestine, or large intestine can occur at any time in patients treated with NSAIDs, with or without symptoms. Mild upper GI problems such as dyspepsia are common and can occur at any time during treatment. Therefore, physicians and patients should be alert to ulceration or bleeding, even in the absence of prior GI symptoms. Patients should be counseled about the signs and/or symptoms of serious GI toxicity and what to do if they occur. Although the benefit of periodic laboratory observations has not yet been proven, adequate evaluation has not been made. Only one in five patients who develop a serious GI adverse event during treatment with a nonsteroidal anti-inflammatory drug is symptomatic. Upper GI ulcers, major bleeding, or perforations due to NSAIDs appear to occur in approximately 1% of patients treated for 3 to 6 months compared to approximately 2% to 4% of patients treated for one year. The persistence of these trends over time increases the likelihood that a patient will develop a serious GI event at any stage of treatment. However, even short-term treatment is not without risk.

Extreme caution should be exercised when prescribing NSAIDs to patients with a prior history of ulcer disease or GI bleeding.

Most spontaneous reports of fatal GI events occur in elderly and frail patients; therefore, particular care should be taken when treating this population. **To minimize the potential risk of an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** Alternative treatments that do not include nonsteroidal anti-inflammatory drugs should be considered in high-risk patients.

Studies have shown that patients using NSAIDs and with a prior history of peptic ulcer and/or GI bleeding are 10 times more likely to develop GI bleeding compared to patients without these risk factors. In addition to a history of ulcer, pharmacoepidemiological studies have identified numerous other concomitant and comorbid conditions that may increase the risk of GI bleeding, such as: use of aspirin, treatment with oral corticosteroids, treatment with anticoagulants or selective serotonin reuptake inhibitors, prolongation of treatment with NSAIDs, smoking drinking, alcohol dependence, advanced age, and poor general health.

Renal effects:

Long-term use of NSAIDs has resulted in renal papillary necrosis and other renal damage. As with other NSAIDs, long-term administration of MAXIMUS has resulted in renal papillary necrosis and other changes in the renal medulla. A second form of renal toxicity has been seen in patients in whom renal prostaglandins play a compensatory role in maintaining renal

perfusion. Administration of an NSAID in these patients may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may trigger overt renal decompensation. Patients at greatest risk for this reaction are those with kidney failure, heart failure or liver failure, as well as those taking diuretics or ACE (angiotensin converting enzyme) inhibitors, and the elderly. After discontinuation of NSAID therapy, the state of pre-treatment is usually restored.
In clinical studies, the elimination half-life of flurbiprofen was not changed in patients with renal impairment. The main route of elimination of flurbiprofen metabolites is the kidneys. Decreased elimination of 4'-hydroxy-flurbiprofen has occurred in patients with moderate to severe renal impairment. Therefore, in patients with significantly reduced renal function, dose reduction may be required to prevent accumulation of flurbiprofen metabolites. Such patients should be closely monitored.

Advanced kidney disease:
MAXIMUS treatment is not recommended in patients with advanced kidney disease. However, if initiation of treatment with an NSAID is mandatory, close monitoring of the patient's renal function is recommended (see Special Warnings and Special Precautions for Use - Renal Effects).

Anaphylactoid reactions:
As with other NSAIDs, MAXIMUS can cause anaphylactoid reactions in patients with no known prior exposure. Flurbiprofen should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who have rhinitis with or without nasal polyps, or who exhibit severe and potentially fatal bronchospasm after taking aspirin or other NSAIDs. (see Contraindications, Special warnings and precautions for use - Pre-existing asthma). If an anaphylactoid reaction occurs, the patient should receive immediate emergency treatment.

Skin effects:
Serious skin reactions, some of them fatal, such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely with the use of NSAIDs, including flurbiprofen. These serious events can occur without warning. Patients should be informed of the signs and symptoms of serious skin reactions and flurbiprofen should be discontinued at the first occurrence of skin rash or any sign of hypersensitivity.

Measures

Hepatic effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including MAXIMUS. These laboratory abnormalities may progress, remain unchanged, or resolve spontaneously with continued treatment. Significant elevations of ALT and AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis and hepatic failure, some with fatal outcome, have been reported.

A patient with signs and/or symptoms indicative of hepatic failure or with abnormal liver test values should be evaluated for the development of a more severe hepatic reaction during treatment with MAXIMUS. MAXIMUS therapy should be discontinued if clinical signs and symptoms indicative of liver disease develop or if systemic manifestations (eg, eosinophilia, rash, etc.) occur.

Hematological effects:

Anemia is sometimes seen in patients taking NSAIDs, including MAXIMUS. This may be due to fluid retention, GI blood loss, or an unspecified effect on erythropoiesis. Patients on long-term treatment with NSAIDs, including MAXIMUS, should have their hemoglobin and hematocrit levels checked regularly if they show any signs or symptoms of anemia.

NSAIDs have been shown to prolong bleeding time by inhibiting platelet aggregation in some patients. In contrast to aspirin, their effects on platelet function are qualitatively less, of shorter duration, and reversible. MAXIMUS generally does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Patients with pre-existing coagulation disorders or those taking anticoagulants and who may be adversely affected by platelet function changes should be carefully monitored while using MAXIMUS.

Pre-existing asthma:

Asthmatic patients may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma can lead to severe bronchospasm, which can be fatal. Since cross-reactions, including bronchospasm, between aspirin and other NSAIDs have been reported in such aspirin-sensitive patients, MAXIMUS should not be used in patients with this type of aspirin sensitivity and should be used with caution in patients with pre-existing asthma. (see section 4.3 Contraindications)

Vision changes:

Cases of blurred vision and/or decreased vision have been reported during the use of MAXIMUS and other nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with eye complaints should undergo an eye examination.

Systemic lupus erythematosus (SLE) and other connective tissue diseases:

Patients with SLE and mixed connective tissue disease are at increased risk of aseptic meningitis.

Laboratory tests:

Because severe GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor patients for signs or symptoms of GI bleeding. Complete blood count and biochemistry profiles of patients on long-term NSAID therapy should be checked periodically. Flurbiprofen should be discontinued if clinical signs and symptoms consistent with liver or renal disease develop, or if systemic manifestations (eg, eosinophilia, rash, etc.) occur.

Impaired female fertility:

Flurbiprofen may impair female fertility. Therefore, it is not recommended for women who want to become pregnant.

Concomitant use with oral anticoagulant drugs:

Concomitant use of NSAIDs, including flurbiprofen, and oral anticoagulants should be given with caution, as they increase the risk of GI or non-GI bleeding. Oral anticoagulants include the warfarin/coumarin type and newly developed oral anticoagulants (eg apixaban, dabigatran, rivaroxaban). Anticoagulant/INR should be monitored in patients using warfarin/coumarin-type anticoagulants (see Section 4.5).

Additional information on special populations:

Pediatric population:

There are no data on its use in children.

Geriatric population:
As with other NSAIDs, caution should be exercised when treating the elderly (65 years and older). Gastrointestinal complaints such as ulceration, bleeding, gas, bloating and abdominal pain are more common in elderly patients. To minimize the potential risk of gastrointestinal events, the lowest effective dose should be used for the shortest possible duration. (See section 4.4 - Special warnings and precautions for use - Gastrointestinal (GI) effects) Likewise, elderly patients are at higher risk of developing renal decompensation. (see section 4.4 - Special warnings and precautions for use - Renal effects)

MAXIMUS contains 26 mg of lactose monohydrate. It should not be used in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet; Considering the amount of sodium it contains, no side effects are expected.

4.5 Interaction with other medicinal products and other forms of interaction
Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB):
Current reports indicate that NSAIDs: diuretics and other antihypertensive drugs including ACE inhibitors, ARBs and beta blockers may reduce the efficacy. In patients with compromised renal function (e.g. dehydrated patients or the elderly with reduced renal function), concomitant use of an ACE inhibitor or an ARB and/or diuretics with a cyclooxygenase inhibitor may increase deterioration of renal function, including the possibility of acute renal failure, which is generally reversible. . The occurrence of these interactions should be considered in patients taking flurbiprofen with an ACE inhibitor or ARB and/or diuretics.
Therefore, caution should be exercised in the concomitant use of these drugs, especially in elderly patients. Patients should take adequate water and renal functions should be monitored periodically at the beginning of the concomitant treatment and afterwards.

Anticoagulants:
Patients taking warfarin with NSAIDs are at a greater risk of serious clinical bleeding than those taking either drug alone. Physicians should be cautious when administering MAXIMUS to patients taking warfarin or other anticoagulants.

Aspirin:
Concomitant administration of aspirin reduces serum flurbiprofen concentrations. The clinical significance of this interaction is unknown; however, as with other NSAIDs, co-administration of MAXIMUS and aspirin is not recommended.

Beta-adrenergic blocking agents:
Although flurbiprofen reduced the hypotensive effect of propranolol, no such effect was seen with atenolol. The mechanism underlying this interaction is unknown. Patients receiving both flurbiprofen and a beta-blocker should be monitored for an adequate hypotensive effect.

Diuretics:
NSAIDs may reduce the natriuretic effect of furosemide and thiazides in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Patients taking diuretic drugs in combination with MAXIMUS should be closely monitored for signs of renal impairment (see Special warnings and precautions for use - Renal effects) and to ensure the desired diuretic effect is achieved.
Lithium:
NSAIDs led to an increase in plasma lithium levels and a decrease in renal lithium clearance. Minimum lithium concentration increased by 15% and renal clearance decreased by 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by NSAIDs. Therefore, patients should be closely monitored for lithium toxicity when lithium is co-administered with NSAIDs.

Methotrexate:
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney sections. This may indicate that these drugs may increase the toxicity of methotrexate. Particularly in patients receiving high-dose methotrexate, caution should be exercised when NSAIDs are administered together with methotrexate, as the use of NSAIDs may lead to increased plasma levels of methotrexate.

Corticosteroids:
There is an increased risk of gastrointestinal ulceration or bleeding.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding

Cimetidine, Ranitidine:
Except for a small but statistically significant increase, it did not affect the pharmacokinetics of flurbiprofen.

Digoxin:
Concomitant use of flurbiprofen and digoxin did not alter the steady-state serum concentrations of either drug. However, NSAIDs can exacerbate heart failure, decrease GFR (glomerular filtration rate), and increase plasma levels of glycosides.

Oral hypoglycemic agents:
Although there was a slight decrease in blood glucose concentrations during co-administration of flurbiprofen with hypoglycemic agents, no signs or symptoms of hypoglycaemia were observed.

Quinolone antibiotics:
They may increase the risk of convulsions when taken with flurbiprofen.

Caution should be exercised when NSAIDs are co-administered with zidovudine, ticlopidine, tacrolimus and cyclosporine.

Tacrolimus:
An increased risk of nephrotoxicity may be observed when NSAIDs are used together with tacrolimus.

Cyclosporine:
COX inhibitors such as flurbiprofen increase the risk of nephrotoxicity of cyclosporine due to their effects on renal prostaglandins.

Additional information on special populations

Pediatric population:

Data not available.

Geriatric population:

Antacids: Antacid suspensions caused a reduction in the rate of absorption, but not in the amount of flurbiprofen absorption when used in geriatric subjects.

4.6 Pregnancy and lactation

General advice

Pregnancy Category is 1. and 2. trimester: C; 3. Trimester is D.

Women of childbearing potential/Contraception

There is no data requiring contraception during the use of MAXIMUS in women of childbearing potential.

Pregnancy period

No developmental abnormalities were found in reproductive studies in mice and rabbits. However, animal reproduction studies are not always sufficient to predict effects in humans. There are no adequate and well-controlled studies in pregnant women. It can be used if the potential benefit of MAXIMUS can offset the potential risk to the fetus.

Inhibition of prostaglandin synthesis may adversely affect pregnancy. Data from epidemiological studies show that prostaglandin synthesis inhibitors used in early pregnancy cause an increased risk of spontaneous abortion. An increase in pre- and post-implantation losses has been demonstrated in animals as a result of administration of a prostaglandin synthesis inhibitor.

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), their use in the late stages of pregnancy (from 6 months) should be avoided.

Reproductive ability/fertility

In studies in rats with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, dystocia, delayed birth, and reduced surviving offspring have occurred. The effects of MAXIMUS on postpartum and childbirth in pregnant women are unknown.

Because of its mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which is associated with reversible infertility in some women. In women who have difficulty conceiving or are being studied for infertility, discontinuation of NSAIDs, including flurbiprofen, should be considered.

Lactation period

Flurbiprofen concentrations in breast milk and plasma indicate that a breastfed infant of a mother using MAXIMUS 200 mg/day can receive approximately 0.10 mg of flurbiprofen per day. Because of the potential adverse effects of prostaglandin-inhibiting drugs on infants, a decision must be made between discontinuing breastfeeding or discontinuing the drug, taking into account the benefit to the mother.

4.7 Effects on ability to drive and use machines

NSAID users may experience side effects such as fatigue, sleepiness, restlessness and visual disturbances after taking the drug. Therefore, vehicles and machinery should not be used when such effects occur.

4.8 Undesirable effects

The following system has been used to classify unwanted side effects.

Very common (≥1 / 10), common (≥1 / 100 to <1/10), uncommon (≥1 / 1.000 to <1/100), rare (≥1 / 10.000 to <1 / 1.000), very rare (<1 / 10.000), unknown (can not be predicted from the given data).

Adverse events in patients using MAXIMUS or other or other NSAIDs:

Events reported in patients using MAXIMUS				
	Common	Uncommon	Rare	Unknown
Infections and	Rhinitis,			

infestations	Urinary tract infection signs and symptoms			
Blood and lymphatic system diseases		Iron deficiency anemia		Inhibition of platelet aggregation
Immune system diseases			Anaphylactic reactions	
Metabolism and nutritional diseases	Changes in body weight	Hyperuricemia Fluid retention		
Psychiatric diseases	Anxiety Depression Insomnia Irritability	Confusion		
Nervous system diseases	Amnesia Dizziness Headache Increase in reflexes Somnolence Shivering	Ataxia Cerebrovascular ischemia Paresthesia Parosmia		
Eye diseases	Changes in vision	Conjunctivitis		
Ear and inner ear diseases	Tinnitus			
Cardiac diseases		Heart failure	myocardial infarction	
Vascular		Vascular diseases		

diseases		Vasodilation Hypertension		
Respiratory, thoracic and mediastinal disorders		Asthma Epistaxis		
Gastrointestinal diseases	Abdominal pain Constipation Diarrhea dyspepsia Gas GI bleeding Nausea vomiting	Bloody diarrhea Esophageal disease Gastritis Hematemesis Peptic ulcer disease Stomatitis Gastrointestinal ulcer	Gastrointestinal perforation	
Hepatobiliary diseases		Hepatitis		
Skin and subcutaneous tissue diseases	Debris	Angioedema Eczema Itching Urticaria		
Kidney and urinary tract diseases		Hematuria Kidney failure	Glomerulonephritis, Renal papillary necrosis Nephrotic syndrome	
General disorders and disorders regarding	Asthenia Edema Weakness	Chill Fever		

administration site conditions				
Studies	Elevated liver enzymes	Decreased hemoglobin and hematocrit levels		

The following adverse events are mainly derived from worldwide post-marketing experience and literature. Precise frequency estimation is often not possible.

	Side effects
Blood and lymphatic system diseases	Aplastic anemia, hemolytic anemia, thrombocytopenia
Immune system diseases	Anaphylaxis
nervous system diseases	Aseptic meningitis
Gastrointestinal diseases	Colitis, inflammatory bowel disease exacerbation, small bowel inflammation with loss of blood and protein
Hepatobiliary diseases	Cholestatic and non-cholestatic jaundice
Skin and subcutaneous tissue diseases	Exfoliative dermatitis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrosis
Kidney and urinary tract diseases	Interstitial nephritis

4.9 Overdose and its treatment

Symptoms after acute overdose with NSAIDs are generally limited to lethargy, drowsiness, nausea, vomiting, impaired mental status, low muscle tone, headache, diplopia, elevated liver enzymes, respiratory depression and epigastric pain, and are reversible with supportive treatment. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory

depression and coma may also occur, but are rare. Anaphylactoid reactions have been reported after the use of NSAIDs in the treatment, and they may also occur after overdose.

A patient taking an overdose of an NSAID should receive symptomatic and supportive treatment. There is no specific antidote. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) within 4 hours of ingestion in patients with symptoms or who have received a very high dose (5 to 10 times the normal dose) and/or osmotic cathartic may be indicated. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be beneficial due to high protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-selective COX inhibitors

ATC code: M01AE09

MAXIMUS contains flurbiprofen, a non-steroidal anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic effects. The mechanism of action of MAXIMUS, like other NSAIDs, is not completely understood and is thought to be related to inhibition of prostaglandin synthetase.

5.2 Pharmacokinetic properties

General Properties

Absorbation:

Flurbiprofen The average oral bioavailability of flurbiprofen in 100 mg is 96% compared to the oral solution. Flurbiprofen is rapidly and nonstereoselectively absorbed from MAXIMUS, with peak plasma concentrations reached in approximately 2 hours (see Table 2). Taking MAXIMUS with food or antacids may change the rate of absorption of flurbiprofen, but not the rate of absorption. Ranitidine has no effect on the rate and rate of absorption of flurbiprofen.

Distribution:

The virtual volume of distribution (Vz/F) of both R- and S-flurbiprofen is approximately 0.12 L/Kg. Both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Binding to plasma proteins is relatively constant at typical mean steady-state concentrations (≤10 µg/ml) achieved with recommended doses.

Biotransformation:

Numerous metabolites of flurbiprofen have been detected in human plasma and urine. These metabolites include 4'-hydroxy-flurbiprofen, 3',4'-dihydroxy-flurbiprofen, 3'-hydroxy-4'-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other arylpropionic acid derivatives (eg ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen occurs minimally. In vitro studies have shown that cytochrome P450 2C9 plays an important role in the metabolism of 4'-hydroxyflurbiprofen, the main metabolite of flurbiprofen. The 4'-hydroxyflurbiprofen metabolite showed little anti-inflammatory activity in animal models of inflammation. Flurbiprofen does not induce enzymes that alter its metabolism. Total plasma clearance of unbound flurbiprofen is not stereoselective and is dose independent when used within the therapeutic range.

Flurbiprofen biotransformation is predominantly mediated by cytochrome P450 2C9 in the liver. Based on previous exposure to other cytochrome P450 2C9 substrates, flurbiprofen should be used with caution in patients with known or suspected slow cytochrome P450 2C9 metabolisers. Because these patients may have abnormal plasma levels due to low metabolic clearance.

Elimination:

Less than 3% of flurbiprofen is excreted unchanged in the urine after the use of MAXIMUS, and approximately 70% of the dose eliminated in the urine is the parent drug and its metabolites. Because renal elimination is an important route of elimination of flurbiprofen metabolites, dose adjustment may be required in patients with moderate to severe renal impairment to prevent accumulation of flurbiprofen metabolites. The mean terminal half-lives (t1/2) of R- and S-flurbiprofen are 4.7 and 5.7 hours, respectively, and are similar to each other. Flurbiprofen accumulation was minimal after multiple MAXIMUS dosing.

Linearity/ Non-linearity:

Dose proportionality has not been evaluated.

Characteristics in patients

Liver failure:

Flurbiprofen is >90% metabolized by the liver, so patients with liver disease may need to reduce doses of MAXIMUS compared to patients with normal liver function. However, the pharmacokinetics of R- and S-flurbiprofen after a single dose of 200 mg MAXIMUS were similar in alcoholic cirrhosis patients (N=8) and young healthy volunteers (N=8).

The plasma protein binding of flurbiprofen may be reduced in patients with liver disease and serum albumin concentrations below 3.1 g/dL.

Kidney failure:

Although renal clearance is an important route of excretion of flurbiprofen metabolites, it is a poor excretion pathway for unchanged flurbiprofen (≤3% of total clearance) to kidney in healthy volunteers (N=6.5, 50 mg single dose) with normal clearances of unbound R- and S-flurbiprofen. There was no significant difference between patients with insufficiency (N=8, insulin clearances ranging from 11 to 43 mL/min, multiple doses of 50 mg). The plasma protein binding of flurbiprofen may be decreased in patients with renal impairment and serum albumin concentrations below 3.9 g/dL. Elimination of flurbiprofen metabolites may be reduced in patients with renal impairment.

Flurbiprofen does not leave the blood to a significant extent in patients undergoing continuous ambulatory peritoneal dialysis.

Pediatric population:

The pharmacokinetics of flurbiprofen in pediatric patients have not been studied.

Geriatric population:

The pharmacokinetics of the drug were found to be similar in geriatric arthritis, young arthritis patients and healthy individuals who received MAXIMUS as a single or multiple dose.

5.3 Preclinical safety data

Carcinogenicity, reproductive and teratology studies have been conducted. Although these studies did not find carcinogenic, teratogenic or adverse reproductive effects, see section 4.6 for effects on fertility/fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose 200
Croscarmellose sodium (Ac-Di-Sol)
Colloidal silicon dioxide (Aerosil 200)
Lactose monohydrate (Tablettose) (obtained from cow's milk)
Magnesium Stearate
Talc
Opadry II 85G34747 pink

6.2 Incompatibilities

It does not have any known incompatibilities.

6.3 Shelf Life

36 months.

6.4 Special precautions for storage

It should be kept in below 25°C room temperature.

6.5 Nature and contents of container

Each film-coated tablet contains 100 mg of flurbiprofen and tablets are presented in blister packs of 15 and 30 tablets.

MAXIMUS 100 mg tablets packed in blister packs.

Packaging components are as follows:

1. Transparent PVC / PVDC

2. Aluminium foil

6.6 Instructions for use and handling

Unused products or waste materials are defined in the "Medical Waste Control Regulation" and shall be disposed of in accordance with the "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORISATION HOLDER

Drogsan İlaçları Sanayi ve Ticaret A.Ş.
Oğuzlar Mah. 1370. Sk. No: 7/3
06520 Balgat-Ankara / Turkey

8. MARKETING AUTHORIZATION NUMBER

210/49 (in Turkey)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First Authorization Date: 29.12.2006 (in Turkey)

Authorization Renewal Date:27.11.2013 (in Turkey)

10. DATE OF REVISION OF THE TEXT

09.06.2020