methotrexate infusion treatment in high dosages should not be applied. Excretion of the drug out of the body by cutting the meloxicam should be waited. And, in patients receiving chronic methotrexate treatment in low dosage, blood levels and kidney function should be observed closely.
In case of common usage, NSAIDs may increase nephrotoxicity by decreasing renal elimination of cyclosporine.
In clinical studies, it is has been reported that NSAIDs reduce natriuretic effects of furosemide and thiazide diuretics. However, there has not been such an effect in studies with meloxicam. Nevertheless, MEXICAM should be used in diuretic patients with care.

DOSAGE and ADMINISTRATION :
The lowest effective dose of MEXICAM should be used for the shortest duration necessary to control symptoms.
The dose of MEXICAM for treatment of rheumatoid arthritis is 15 mg once daily. According to the therapeutic response, the dose may be reduced to 7.5 mg/day.
The dose for treatment of osteoarthrosis is 7.5 mg once daily. According to the therapeutic response, the dose may be increased to 15 mg/day. The dose for treatment of ankylosing spondylitis is 15 mg once daily. The maximum recommended daily dose of MEXICAM is 15 mg.
If the tablet and suppository dosage forms are administered together, the total dose should not exceed 15 mg.
The starting dose is 7.5 mg daily for the patients who have high risk of side effects and undesirable effects.Total daily dose should not exceed 7.5 mg for the patients who have severe renal impairment.
MEXICAM tablets should be taken with water or another liquid, during a meal.

OVERDOSE :
In cases of acute overdose, gastric lavage or emesis followed by activated charcoal is performed. Gastric lavage performed within one hour after overdose and activated charcoal administered within 1-2 hours after overdose have little benefit. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gram oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalinization of urine, hemodialysis and hemoperfusion may not be useful due to high protein binding.

STORAGE :
Keep out of the reach of children. Store at room temperature below 25°C in original package. Protect from the light and store at dry place.

HOW SUPPLIED :
MEXICAM 15 mg Fort Tablet, blisters of 30 tablets and 10 tablets

PRODUCT LICENCE HOLDER :
The holder of trade mark and Marketing Authorization is
"BIOACTIVE T, UNITED KINGDOM.

BioActiveT United Kingdom

2200654-A

MEXICAM 15 mg FORT TABLET

FORMULA : Each tablet contains 15 mg Meloxicam.

PHARMACOLOGICAL PROPERTIES :
Pharmacodynamic Properties :
Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) from the enoleic acid of the oxicam family that exhibits antiinflammatory, analgesic, and antipyretic activities.
MEXICAM is an oxicam group nonsteroid anti-inflammatory drug out of enoleic acid class and has anti-inflammatory and antipyretic effects (NSAID). It potently inhibits inflammation symptoms in empirical inflammation models. This effect results from its inhibition of cyclooxygenase (COX) catalyzing prostaglandin synthesis. However, this effect of meloxicam concentrates on the COX-2 enzyme that is a cyclooxygenase isoform and of which induction is executed through inflammation mediators in the inflammation area more than the COX-I enzyme providing contraceptive prostaglandins in stomach and kidney. As a matter of fact, clinical datum has shown that adverse effects of the meloxicam on the stomach are lower compared with NSAIDs which nonselectively inhibit both COX enzymes.

Pharmacokinetic properties :
Absorption:
The absolute bioavailability of meloxicam was 89% following an oral dose compared with IV injection. Plasma levels are proportional with the administered dose over the range of therapeutic dose. Mean maximum plasma concentration (Cmax) was achieved within 4 to 5 hours when taken under fasted conditions, indicating a prolonged drug absorption. It has a linear pharmacokinetic property without any change at the rate and extent of absorption with multiple dosing. Steady state conditions were reached within 5 days with multiple dosing.
Food and Antacid Effects: Administration of the drug following a high fat food resulted in Cmax being increased by approximately 22% while the extent of absorption was unchanged. The time to maximum concentration (Tmax) was achieved between 5 and 6 hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Based on these results, meloxicam can be administered without regard to timing of meals or concomitant administration of antacids.

Distribution:
The mean volume of distribution (Vss) of meloxicam is 10 L. Meloxicam is ~ 99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of plasma concentration. 90% of meloxicam detected in the plasma was present as unchanged molecule.
Meloxicam concentrations in synovial fluid range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma.
Metabolism:
Meloxicam is almost completely metabolized to four pharmacologically inactive metabolites. The major metabolite, 5-carboxy meloxicam (60% of dose), from P-450 mediated metabolism was formed by oxidation of an intermediate metabolite 5-hydroxymethyl meloxicam (9% of dose). This metabolic pathway is controlled by cytochrome P-450 2C9. Peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively.
Excretion :
Meloxicam excretion is in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). There is significant biliary and/or enteral secretion of the drug. The mean elimination half-life ($t_{\frac{1}{2}}$) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism. Plasma clearance of meloxicam ranges from 7 to 9 mL/min.

Special Populations:
Pediatric Patients: The pharmacokinetics of meloxicam in pediatric patients under 18 years of age have not been investigated.
Geriatric Patients: Elderly males (≥ 65 years of age) exhibited meloxicam plasma concentrations and steady state pharmacokinetics similar to young males. Elderly females (≥ 65 years of age) had a 47% higher AUC values and 32% higher Cmax values as compared to younger females. The adverse event profile was comparable for elderly male and female patient populations. Free plasma fraction was lower in elderly female patients compared to elderly male patients.
Gender: Young females exhibited slightly lower plasma concentrations relative to young males.
Hepatic Insufficiency: Following a single 15 mg dose of meloxicam there was no difference in plasma concentrations in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. No dose adjustment is necessary in mild to moderate hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied.
Renal Insufficiency: Total drug plasma concentration is decreased and total clearance of meloxicam is increased in patients with renal insufficiency.
There is no need for dose adjustment in patients with mild to moderate renal failure (CrCL > 15 mL/min). Patients with severe renal insufficiency have not been adequately studied. The use of drug in subjects with severe renal impairment is not recommended. The free plasma meloxicam fractions were higher in patients with renal failure on hemodialysis in comparison to healthy volunteers. Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable.

INDICATIONS :
MEXICAM, is indicated for symptomatic treatment of rheumatoid arthritis, osteoarthrosis (arthrosis, degenerative joint disease) and ankylosing spondylitis.

CONTRAINDICATIONS :
MEXICAM is contraindicated in the following situations;
In patients with known hypersensitivity to meloxicam or to any of the excipients of the tablet,
In patients with hypersensitivity to acetylsalicylic acid or other NSAIDs, who have developed signs of asthma, nasal polyps or urticaria following the administration of acetylsalicylic acid or other NSAIDs
Besides, MEXICAM should not be taken in patients with active peptic ulcer, severe hepatic and renal impairment, children and adolescents aged under 15 years of age, pregnant women and nursing mothers.

WARNINGS / PRECAUTIONS :
MEXICAM should not be used in individuals who have an active ulcer illness or suffered from the upper gastrointestinal. If it should be used in the ones who had these illnesses beforehand, an anti-ulcer treatment should be applied. Since prostaglandins are necessary for normal kidney function, inhibition of them may cause acute renal failure in especially hypovolemic patients. Thus, MEXICAM should be used carefully in patients whose effective blood volume decreased and who have a hypovolemia risk, and in case of congestive heart failure, cirrhosis, dehydration, surgical operation, nephrotic syndrome, diuretic usage, and kidney functions should be followed up. NSAIDs (Non-Steroidal Anti-Flammatory Drugs) may rarely cause nephrite, nephrosis, and renal medullar necrosis. In advanced renal failure, the dosage should not exceed 7.5 mg per day. If clearance of the creatine is > 25 ml/min, dosage reduction is not required.

MEXICAM should be used carefully in patients who have hemorrhagic diathesis (hemophilia, coagulation, and platelet function disorders). NSAIDs inhibit platelet aggregation and increase risk of the gastrointestinal hemorrhage and ulceration. Slight and temporary variations may be seen at serum transaminase levels during MEXICAM treatment. In case these are permanent and on the highest degree, the treatment should be quitted. It is not clinically required to reduce the dosage in stabile liver cirrhosis.

2200654-A

If there are diabetes mellitus, alcoholism, oedema, hypertension, hypovolemia, sepsis in old and imbecilic patients, MEXICAM should be used carefully.
Use in Pediatric Patients:
Safety and efficacy of meloxicam have not been determined in patients under 18 years of age.
Use in Geriatric Patients:
As with any NSAID, caution should be exercised in treating the elderly (65 years and older) patients.

Usage in Pregnancy and Lactation:
Pregnancy: Pregnancy Category C.
In experimental researches, congenital malformation and embryo toxicity effects with meloxicam were observed. There are no adequate and well-controlled studies in pregnant women. Meloxicam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation:
In experimental researches, it was determined that meloxicam was excreted in the milk at concentrations higher than those in plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug.

Effect on Driving and Operating Machinery :
There are no specific studies of the ability to drive and use machinery while using MEXICAM. However, when visual disturbances, drowsiness or vertigo occur, it is advisable to refrain from driving and operating machinery while using the drug.

SIDE EFFECTS / ADVERSE REACTIONS :
In clinical trials, following side effects were observed in patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam. Relation of casualty between meloxicam and following side effects has not been determined certainly.
Gastrointestinal system: Nausea, vomiting, abdominal pain, diarrhoea, constipation, dyspepsia, meteorism, gastric and duodenal ulcer, oesophagitis, gastrointestinal hemorrhage, colitis, temporary transaminase or increase of bilirubin.
Cardiovascular system: Oedema, hypertension, palpitation, flushing.
Hematologic: Anemia, leukopenia, thrombocytopenia.
Respiratory: Acute asthma (bronchospasm)
Dermatological: Pruritus, urticaria, skin rash, stomatitis, photosensitization.
Central nervous system: Headache, tinnitus, blurred vision, dizziness.
Urogenital: Increase in serum creatin or urea levels
IN THE EVENT OF AN UNEXPECTED REACTION CONSULT YOUR PHYSICIAN.

DRUG INTERACTIONS AND OTHER INTERACTIONS :
If NSAIDs are given along with the drugs that decrease the number or function of the platelet, constitute hypoprothrombinemia or, of which potential of gastrointestinal ulceration and hemorrahage formation is high, hemorrahage risk increases. Usage of MEXICAM together with salicylates or an NSAID increases GI hemorrahage and ulceration and also does not serve an additional therapeutic purpose. If corticosteroids, corticotrophin, potassium sugar-coated tablets, alcohol are used along with NSAIDs, risk of GI hemorrahage and ulceration increases. When anticoagulants, coumarin or indentation derivatives, heparin, thrombolytic agents (streptokinase, urokinase, alteplase) are given together with NSAIDs, risk of hemorrahage increases.
Since NSAIDs inhibit renal prostaglandin formation, kidney function may decrease. Sodium and water retention may cause a decrease in the effect of the diuretic and antihypertensive drugs. As a result of decrease in blood volume and renal blood flow after diuretic treatment, acute renal failure may emerge. It has been stated that NSAIDs reduce antihypertensive effect of the Angiotensin Converting Enzyme (ADE) inhibitors, when they are used together.
It has been stated that NSAIDs increase lithium concentrations of blood in patients receiving lithium treatment. Blood levels of the lithium should be observed closely in these patients and, if required, dosage adjustment should be done. NSAIDs increase blood's concentration and toxicity by combining methotrexate with protein and reducing renal elimination. In patients receiving meloxicam treatment,