Product Name :	DABIC 7.5
Generic Name :	MELOXICAM TABLETS BP 7.5 MG
MODULE 1	

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DABIC 7.5 (MELOXICAM TABLETS BP 7.5 MG)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition

Each uncoated tablet contains:

Meloxicam BP……7.5 mg

Excipients……q.s

3. PHARMACEUTICAL FORM

Tablet

Light yellow coloured, round shaped, biconvex, uncoated tablet with break-line on one side & plain on another side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short-term symptomatic treatment of exacerbations of osteoarthrosis.
- Long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

4.2 Posology and method of administration

The total daily amount should be taken as a single dose with water or another liquid, during a meal. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

The patient's need for symptomatic relief and response to therapy should be reevaluated periodically, especially in patients with osteoarthritis.

Exacerbations of osteoarthrosis: 7.5 mg once daily.

If necessary, in the absence of improvement, the dose may be increased to 15 mg once daily (one 15 mg tablet).

Rheumatoid arthritis, ankylosing spondylitis: 15 mg once daily (one 15 mg tablet).

According to the therapeutic response the dose may be reduced to 7.5 mg once daily.
DO NOT EXCEED THE DOSE OF 15 MG/DAY.

Special populations

Elderly patients and patients with increased risks for adverse reactions:

The recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risk for adverse reactions should start treatment with 7.5 mg per day.

Renal impairment:

In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day. No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance greater than 25 ml/min)

Hepatic impairment:

No dose reduction is required in patients with mild to moderate hepatic impairment.

Children and adolescents:

This medicinal product should not be used in children and adolescents aged under 16 years.
Meloxicam exists in other dosages which may be more appropriate

Method of administration:

For oral administration only.

4.3 Contraindications

This medicinal product is contraindicated in the following situations:

• Third trimester of pregnancy and lactation.

• Children and adolescents aged under 16 years

• Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, acetylsalicylic acid. This medicinal product should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of acetylsalicylic acid or other NSAIDs.

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

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

• Severely impaired liver function.

• Non-dialysed severe renal failure.

• Gastrointestinal bleeding, history of cerebrovascular bleeding or other bleeding disorders.

• Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. The use of meloxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Meloxicam is not appropriate for the treatment of patients requiring relief from acute pain.

In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

Gastrointestinal effects

Gastrointestinal 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 gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, 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.

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as a curative treatment or given in geriatrics, anticoagulants such as Warfarin or other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount.

When gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, the product 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.

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.

Skin Reactions

Life-threatening cutaneous reactions including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported with the use of meloxicam. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first month of treatment. If symptoms or signs of exfoliative dermatitis, SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, or any other sign of hypersensitivity, meloxicam treatment should be discontinued. The best results in managing these reactions come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed exfoliative dermatitis, SJS or TEN with the use of meloxicam, meloxicam must not be re-started in this patient at any time.

Parameters of liver and renal function

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen.

The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken.

Functional renal failure

NSAIDS, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose dependent. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors:

- Elderly
- Concomitant treatments such as ACE inhibitors, Angiotensin-II-antagonists, sartans, diuretics
- Hypovolaemia (whatever the cause)
- Congestive heart failure
- Nephrotic syndrome
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin < 25g/l or Child-Pugh score ≥ 10).

In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

The dose of meloxicam in patients with end-stage renal failure on haemodialysis should not be higher than 7.5mg. No dose reduction is required in patients with mild to moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 ml/min).

Sodium, potassium and water retention

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Furthermore, a decrease of the antihypertensive effect of antihypertensive drugs can occur.

Consequently, oedema, cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. Clinical monitoring is therefore necessary for patients at risk.

Hypokalaemia

Hypokalaemia can be associated with diabetes or concomitant treatment known to increase kalaemia. Regular monitoring of potassium values should be performed in such cases.

Lactose

If you have been told by doctor that you have intolerance to some sugar, contact your doctor before taking this medicinal product**.**

Paediatric population: This medicine is not use for Paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Other NSAIDs, including salicylates: Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin.

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

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function before initiation of concomitant therapy, and periodically thereafter.

Other antihypertensive drugs (e.g. Beta-blockers): As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Ciclosporin: Nephrotoxicity of ciclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly. Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding.
Intrauterine devices: NSAIDs have been reported to decrease the efficacy of intrauterine devices. A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation. Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs).
Lithium: NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.
Methotrexate: NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended.
The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.
Although the pharmacokinetics of methotrexate (15mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.
Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)
Cholestyramine: Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.
CYP3A4 and CYP 2C9 inhibitors, inducers and substrates: Metabolic interactions possible.
No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine and digoxin, but increased serum levels of digoxin may occur.

Additional information on special populations:

Adverse reactions are often less tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Meloxicam, as other NSAIDs, may mask symptoms of an underlying infectious disease.

The use of meloxicam, as with any substance known to inhibit cyclooxygenase/prostaglandin synthesis, may impair 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 meloxicam should be considered.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.6 Fertility, pregnancy and lactation

Pregnancy:

It is advisable to avoid the administration of meloxicam during the first two trimesters of pregnancy.

During the final three months, all prostaglandin synthesis inhibitors may expose the fetus to cardiopulmonary (pulmonary hypertension with premature closure of the ductus arteriosus) and renal toxicity or inhibit the contraction of the uterus. This effect on the uterus has been associated with an increase in the incidence of dystocia and delayed parturition in animals.

Thus all NSAIDs are absolutely contra-indicated during the final three months.

Lactation:

NSAIDs pass into mother’s milk. Administration is contraindicated, as a precautionary measure, in women who are breast feeding.

4.7 Effects on ability to drive and use machines

There are no specific studies on the ability to drive and use machinery. If during the treatment, however, visual disturbances, dizziness, fatigue or any CNS disturbance occur, it is recommended to avoid driving and using machines.

4.8 Undesirable effects

Blood and the lymphatic system disorders:

Anaemia, Disturbances of blood count: leucocytopenia, thrombocytopenia, agranulocytosis.

Immune system disorders:

Anaphylactic/anaphylactoidreactions.

Psychiatric disorders:

Mood disorders, insomnia and nightmares.

Nervous system disorders:

Light-headedness, headache, Vertigo, tinnitus, drowsiness, Confusion.

Eye disorders:

Visual disturbances including blurred vision.

Cardiac and vascular disorders:

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

Vascular disorders:

Increase in blood pressure, flushes.

Respiratory, thoracic and mediastinal disorders:

Onset of asthma attacks in certain individuals allergic to aspirin or other NSAIDs.

Gastrointestinal disorders:

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur, Nausea,

vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

Hepato-biliary disorders:

Transitory disturbance of liver function test, Hepatitis.

Skin and subcutaneous tissue disorders:

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Renal and urinary disorders:

Disturbances of laboratory tests investigating renal function, renal failure.

General disorders and administration site conditions

Oedema including oedema of the lower limbs.

4.9 Overdose

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

Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}: Anti-Inflammatory and antirheumatic products, nonsteroids; Oxicams.

ATC code: M01AC06

Mechanism of action:

Meloxicam is a non-steroidal anti-inflammatory substance (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.

The anti-inflammatory property of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown.

However, there is at least one common mode of action shared by all NSAIDs (including meloxicam): Inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

5.2 Pharmacokinetic properties

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent.

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within two hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets). With multiple dosing, steady state conditions were reached within 3-5 days. Once daily dosing leads to meloxicam plasma concentrations with a relatively small peaktrough fluctuation in the range of 0.4-1.0 μg/ml for 7.5 mg doses and 0.8-2.0 μg/ml for 15 mg doses, respectively (Cmin and Cmax at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within 5-6 hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

Distribution

Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%).

Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11 l. Interindividual variation is the order of 30-40%.

Biotransformation

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose).

In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose, respectively.

Elimination

Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.

The mean elimination half-life is about 20 hours. Total plasma clearance amounts on average to 8 ml/min.

5.3 Preclinical safety data

The toxicological profile of meloxicam has been found in preclinical studies to be identical to that of other NSAIDs: Gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Oral reproductive studies with meloxicam in rats have shown a decrease of ovulations andinhibition of implantations and embryo toxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on a mg/kg dose basis (75 kg person). Foetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. No evidence has been found of any mutagenic effect, neither *in vitro* nor *in vivo*. No carcinogenic risk has been found in the rat and mouse at doses far higher than those used clinically.

Product Name :	DABIC 7.5
Generic Name :	MELOXICAM TABLETS BP 7.5 MG
MODULE 1	

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose

Colloidal anhydrous silica

Maize Starch

Sodium Starch Glycolate

P.V.P. K-30

Isopropyl alcohol

Purified Talc

Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months or expiry of active whichever earlier.

6.4 Special precautions for storage

Store below 30^{o}C. Protect from light and moisture.

6.5 Nature and contents of container

10 Tablets in one Alu-Alu Blister, 1 Alu-Alu Blister in one carton with Insert.

6.6 Special precautions for disposal and other handling

Store in a cool & dry place. Protect from light.

7. Marketing authorisation holder

Applicant:

M.S MARCSON HEALTHCARE LTD.

9, ISAWO RD, AGRIC, IKORODU, LAGOS, NIGERIA

Product Name :	DABIC 7.5
Generic Name :	MELOXICAM TABLETS BP 7.5 MG
MODULE 1	

Manufacture by

OSAKA Pharmaceuticals Pvt. Ltd.
NATIONAL HIGHWAY NO.8,

AT. & POST. SAKARDA,

TA. & DIST. VADODARA

INDIA

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
