SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MELCAM 15 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains
Active substance:
Meloxicam 15 mg
Excipient(s):
Lactose monohydrate 35 mg
Sodium citrate dihydrate 30 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet
Yellow, slightly curved, round tablets with a homogeneous appearance, scored in the middle on one side.
The purpose of the score is to be able to divide the tablet into equal doses. Thus, the tablet can be divided into equal halves of 7.5 mg.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Indicated for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and the treatment of acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
Carefully consider the potential benefits and risks of MELCAM and other treatment options before deciding to use MELCAM. Use the lowest effective dose for the shortest possible duration necessary to control symptoms.

After observation of initial response to MELCAM, the dose and frequency should be adjusted according patient requirement.

- Exacerbation of osteoarthritis: Recommended dose is 7.5 mg/day (half of a 15 mg tablet). The dose may be increased to 15 mg/day if desired effect is not achieved (1 tablet of 15 mg).
- Rheumatoid arthritis, ankylosing spondylitis: Recommended dose is 15 mg/day (1 tablet of 15 mg) (see also additional information on special populations).
  According to the therapeutic response, the dose may be reduced to 7.5 mg daily (half of a 15 mg tablet).
  Acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea: Recommended dose is 7.5 mg/day (half of a 15 mg tablet), dose may be increased to 15 mg/day (1 tablet of 15 mg) if desired effect is not achieved.

DAILY DOSE SHOULD NOT EXCEED 15 mg.

Method of administration:

Administered orally. The total daily dose should be taken as single dose with water or another liquid, during a meal.

Additional information on special populations:
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 (a creatinine clearance of greater than 25 ml/min) (see section 5.2) (see section 4.3 for patients with non-dialyzed severe renal failure).

Hepatic impairment:
No dose reduction is required in patients with mild to moderate liver impairment (see section 5.2) (see section 4.3 for patients with severely impaired liver function).

Pediatric population:
MELCAM should not be used in children and adolescents aged less than 16 years (see section 4.3).

Geriatric population:
The recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg/day (see section 5.2).

Other:
In patients with increased risks of adverse effects, the treatment should be started at a dose of 7.5 mg (see section 4.4).

4.3 Contraindications

MELCAM is contraindicated in treatment of perioperative pain after coronary artery bypass surgery (CABG) (see section 4.4).

MELCAM is contraindicated in:
- In patients with known hypersensitivity to meloxicam, the active substance of MELCAM, and any of the excipients or other substances with a similar action (e.g. acetylsalicylic acid and other NSAIDs) (Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic edema or urticaria-like reactions following administration of acetylsalicylic acid and other NSAIDs); severe, rarely fatal anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.5).
- In treatment of perioperative pain after coronary artery bypass surgery (CABG)
- Third trimester of pregnancy (see section 4.6).
- In patients who have active peptic ulcer/hemorrhage or history of recurrent peptic ulcer/ hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic insufficiency.
- Non-dialyzed severe renal insufficiency.
- Severe heart failure.
- In patients with gastrointestinal bleeding, history of cerebrovascular bleeding or other bleeding disorders.
- In children and adolescents aged less than 16 years.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and precautions for use

Cardiovascular Risk
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Gastrointestinal Risk
NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

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.

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

Patients having history of esophagitis, 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 history of these disorders.

Caution is advised in patients who receive contaminant medications that may increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

MELCAM cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroid.

The pharmacological activity of MELCAM in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

Gastrointestinal effects:
As with all of NSAIDs, fatal gastrointestinal bleeding or ulceration or perforation have been reported at any time during treatment, with or without warning symptoms or a previous history of serious gastro-intestinal events.
Only 1 in 5 patients, who develop a serious upper gastrointestinal adverse event on NSAID therapy, is symptomatic. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs

occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short-term therapy is not without risk.

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 hemorrhage 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 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 curative treatment or given in geriatrics), anticoagulants such as warfarin, and other NSAIDs, including acetylsalicylic acid given at anti-inflammatory doses (≥1 g as single intake or ≥3 g as total daily amount) (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, 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). Patients with a prior history of peptic ulcer disease or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a gastrointestinal bleed compared to patients with neither of these risk factors. Other factors that increase the risk for gastrointestinal bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, and use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal gastrointestinal events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize potential risk for an adverse gastrointestinal event in patients treated with NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected. This should include discontinuation of the NSAID until a serious gastrointestinal event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Cardiovascular and cerebrovascular effects:
As fluid retention and edema associated with NSAIDs therapy have been reported, appropriate monitoring and advice are required for patients with history of hypertension and/or mild to moderate congestive heart failure history.

Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with meloxicam.

Clinical trials of several COX-2 selective and non-selective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective or non-selective, may have a similar risk. Patients with known cardiovascular disease or risk factors for these diseases may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs or symptoms of serious cardiovascular events and the steps to take if they occur.

NSAIDs, including MELCAM, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including MELCAM, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus, and smoking).

There is no consistent proof that concomitant use of meloxicam and acetylsalicylic acid reduces increased risk of serious cardiovascular thrombotic event associated with use of NSAIDs. Concomitant use of acetylsalicylic acid and NSAID increases risk of serious gastrointestinal events (see above *"Gastrointestinal effects"* section)

In two large, controlled clinical trials carried out with COX-2 selective NSAID for treatment of the pain occurring in 10-14 days following coronary artery bypass graft (CABG) surgery, increase has been observed in frequency of myocardial infarction and stroke (see section 4.3.).

Skin reactions:
As with all NSAIDs, including meloxicam, serious skin reactions were very rarely reported such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal (see section 4.8). These serious events may occur without warning. It is understood that patients are at the highest risk in early period of the treatment regarding the reactions, and in most events, reactions occur in the first month of the treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and use of MELCAM should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hepatic effects:
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAID including meloxicam. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or 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, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes

have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MELCAM. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), MELCAM should be discontinued.

Hematologic effects:
Anemia is sometimes seen in patients receiving NSAID, including MELCAM. This may be due to fluid retention, occult or gross gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAID, including MELCAM, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, NSAIDs effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving MELCAM who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Renal effects:
Long-term administration of NSAIDs has developed in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decomposition. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretic and ACE inhibitor, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

NSAIDs may cause rarely interstitial nephritis, glomerulonephritis, renal modular necrosis or necrotic syndrome. The dose of meloxicam in patients with end-stage renal failure on hemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (creatinine clearance >25 ml/min).

No data obtained in controlled clinical trials is available regarding use of meloxicam in patients with improved renal diseases. Therefore, MELCAM is not advised to be used in these patients. If treatment with MELCAM has to be commenced, patient should be closely monitored regarding its renal functions.

Anaphylactoid reactions:
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to MELCAM. MELCAM 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 who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see below: *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Preexisting Asthma:

Patients with asthma may have aspirin-sensitive asthma, the use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, MELCAM should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Sodium, potassium, 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 (see section 4.5). Consequently, edema, cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. Clinical monitoring is therefore necessary for patients at risk (see sections 4.2 and 4.3).

Hyperkalemia:
Hyperkalemia can be favored by diabetes or concomitant treatment known to increase kalemia (see section 4.5). Regular monitoring of potassium values should be performed in such cases.

Laboratory tests:
As with most of NSAID, besides decreases in serum transaminase levels, serum bilirubin or other liver function parameters at times, decreases in serum creatinine, blood urea nitrogen levels, and other laboratory abnormalities have been reported.

Because serious gastrointestinal tract ulceration and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of gastrointestinal bleeding. Patients on long-term treatment with NSAID should have their complete blood counts and a biochemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash) or if abnormal liver tests persist or worsen, MELCAM should be discontinued.

Other warnings and precautions:
Adverse reactions are often less well 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) (see section 4.2).

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

Meloxicam, as with any other drugs 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.

In late pregnancy, as with other NSAIDs, use of MELCAM should be also avoided because it may cause premature closure of the ductus arteriosus (see section 4.6).

This medicinal product contains 35 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet; no sodium-related side effect is expected in this dose.

4.5 Interactions with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

- Pharmacodynamic Interactions:

Other NSAIDs and acetylsalicylic acid ≥3 g/day:
When MELCAM is used as contaminant with acetylsalicylic acid protein binding rate reduces, although free meloxicam clearance does not change. Clinical importance of this interaction is not known. Furthermore, combination with other NSAIDs, including acetylsalicylic acid given at anti-inflammatory doses (≥1 g as single intake or ≥3 g as total daily amount) is not recommended as it increases likelihood of adverse effects (see section 4.4).

Corticosteroids:
The concomitant use with corticosteroids requests caution because of an increased risk of bleeding or gastrointestinal ulceration.

Anticoagulant, heparin (administered in geriatrics or at curative doses):
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anti-coagulants, such as warfarin. The concomitant use of NSAIDs and anticoagulants or heparin administered in the elderly or at curative dose is not recommended (see section 4.4).

In the remaining patients using heparin caution is necessary due to an increased bleeding risk.

Careful monitoring of the INR (International normalized ratio) is required if it is impossible to avoid such combination.

Thrombolytics and antiplatelet medicines:
Risk of bleeding increases because of inhibition of platelet function and damage to the gastroduodenal mucosa (see section 4.4)

Selective serotonin reuptake inhibitors (SSRIs):
Risk of gastrointestinal bleeding increases (see section 4.4)

Serotonin/norepinephrine reuptake inhibitors (SNRIs):
NSAIDs increase effect of antiplatelets (not selective).

Diuretics, ACE inhibitors and Angiotensin-II receptor antagonists:
Clinical trials and post-marketing observations have showed that meloxicam may decrease natriuretic effects of furosemide and thiazide. This response is attributed to inhibition of renal prostaglandin synthesis.

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 co-administration of an ACE inhibitor or Angiotensin-II receptors antagonist and agents that inhibit cyclo-oxygenase 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 after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).

Other antihypertensive drugs (e.g. beta-blockers):
A decrease of the antihypertensive effect of beta-blockers due to inhibition of prostaglandins with vasodilatory effect can occur.

Calcineurin inhibitors (e.g. cyclosporin, tacrolimus):
Nephrotoxicity of calcineurin inhibitors 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.

Intrauterine devices:
NSAIDs have been reported to decrease the efficacy of intrauterine devices; however, it has not been positively approved.

- Pharmacokinetic interactions (effect of meloxicam on the pharmacokinetics of other medicines):

Lithium:
NSAIDs have been reported to increase blood lithium levels to an extent toxic values thereby it reduces renal excretion of lithium. The mean minimum lithium concentration increased by 15%; but renal clearance decreased by 20%. These effects are attributed to inhibition of renal prostaglandin synthesis by NSAIDs. The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination appears necessary, lithium plasma levels 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 (>15 mg/week) the concomitant use of NSAIDs is not recommended (see section 4.4).

The abovementioned risk of an interaction between NSAIDs and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with renal dysfunction. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAIDs 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 (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the hematological toxicity of methotrexate can be amplified by treatment with NSAID (see above) (see section 4.8).

- Pharmacokinetic interactions (effect of other medicines 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 hr. This interaction is of clinical significance.

No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine and digoxin.

- Interactions with alcohol/food products/herbal products:

Alcohol:
It should not be used with alcohol as it may increase gastric mucosal irritation.

Interactions with food products/herbal products:
During treatment with meloxicam, products containing alfalfa (lucerne), anise, cranberry, fucus (bladder wrack), bromelain, cat's claw, celery, matricaria chamomilla, cholio, cordyceps mushroom, dong quai (Chinese angelica/*Angelica sinensis*), primula, fenugreek, tanacetum parthenium, garlic, ginger, *Ginkgo biloba*, ginseng (American, Panax, Siberia), grape seed, green tea, gugal (guggul), aesculus hippocastanum, horse radish, liquorice, opuntia, trifolium pratense (red clover), reishi mushroom, SAMe (S-adenosylmethionine), lemon balm (melissa), curcuma, salix alba should not be consumed as these products have additional anti-platelet activities.

Additional information on special populations:
No additional information on special population is available.

Pediatric population:
There is no interaction study carried out on pediatric population.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category: C/D (3. trimester)

Women of child-bearing potential/Birth control (Contraception)
Meloxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility, thus it is not advised to be used in women attempting to conceive. If meloxicam is being used by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible. Withdrawal of treatment with meloxicam should be considered for women with difficulty of conception or undergoing investigation for infertility.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations (including cardiovascular) have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, meloxicam should not be given unless clearly necessary. If meloxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy all prostaglandin-synthesis inhibitors may expose the fetus to:
- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis

The mother and the neonate, at the end of pregnancy, to:
- Prolongation of bleeding time (an anti-aggregating effect which may occur even at very low doses)
- Inhibition of uterine contractions (resulting in delayed or prolonged labor)

Consequently, meloxicam is contraindicated during the third trimester of pregnancy.

Breast-feeding
While no specific experience exists for meloxicam, NSAIDs are known to pass into mother's milk. Administration therefore is not recommended in lactation.

Fertility
Meloxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility, thus it is not advised to be used in women attempting to conceive.

4.7 Effects on ability to drive and use machines
No specific studies on the effect on the ability to drive and use machineries have been performed. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on these abilities. However, when visual disturbances or drowsiness, dizziness or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

4.8 Undesirable effects

General description:
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) (see section 4.4).

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

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in 27 clinical trials with treatment duration of at least 14 days. The information is based on clinical trials involving 15.197 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablet or capsule over a period of up to twelve months.

Adverse reactions observed during clinical studies have been ranked under headings of frequency:

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); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Uncommon: Anemia
Rare: Blood count abnormal (including differential white cell count), leucopenia, thrombocytopenia

Immune system disorders
Uncommon: Allergic reactions other than anaphylactic or anaphylactoid reactions
Not known: Anaphylactic reaction, anaphylactoid reaction

Psychiatric disorders
Rare: Mood altered, nightmares
Not known: Confusional state, disorientation

Nervous system disorders
Common: Headache
Uncommon: Dizziness, somnolence

Eye disorders
Rare: Visual disturbance including vision blurred, conjunctivitis

Ear and labyrinth disorders
Uncommon: Vertigo
Rare: Tinnitus

Cardiac disorders
Uncommon: Palpitations
Cardiac failure has been reported in association with NSAID treatment.

Vascular disorders
Uncommon: Blood pressure increased (see section 4.4), flushing

Respiratory, thoracic and mediastinal disorders
Rare: Asthma in patients allergic to acetylsalicylic acid or other NSAIDs

Gastrointestinal disorders
Very common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhea
Uncommon: Occult or macroscopic gastrointestinal hemorrhage, stomatitis, gastritis, eructation
Rare: Colitis, gastroduodenal ulcer, esophagitis
Very rare: Gastrointestinal perforation
Gastrointestinal hemorrhage, ulceration or perforation may sometimes be severe and potentially fatal, especially in elderly (see section 4.4).

Hepatobiliary disorders
Uncommon: Hepatic dysfunction (e.g. raised transaminases or bilirubin)
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Angioedema, pruritus, rash
Rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Very rare: Dermatitis bullous, erythema multiforme
Not known: Photosensitivity reaction

Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalemia (see section 4.4.), renal function test abnormal as increased serum creatinine and/or serum urea
Very rare: Acute renal failure especially in patients with risk factors (see section 4.4.)

General disorders and administration site conditions
Common: Edema including edema of the lower limbs.
Agranulocytosis events have been very rarely reported in patients treated with meloxicam and other potentially myelotoxic effective medicines (see section 4.5).

Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds of the class
Organic renal injury probably resulting in acute renal failure: interstitial nephritis, acute tubular necrosis, nephrotic syndrome, and papillary necrosis have been very rarely reported.

4.9 Overdose
Symptoms:
Symptoms of NSAID overdose are limited to lethargy, drowsiness, nausea, and vomiting and epigastric pain. These symptoms 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. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment:
Symptomatic and supportive care following an NSAID overdose must be administered. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given 3 times a day was demonstrated in a clinical trial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Non-steroidal anti-inflammatory products
ATC code: M01AC06

Meloxicam is a NSAID of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.

The anti-inflammatory activity 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

General properties

Absorption:

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

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5-6 hours.

With multiple dosing, steady state conditions were reached within 3-5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough 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 (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state are achieved within 5-6 hours. 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 liters. 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 CYP2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP3A4 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. It occurs to equal extents in urine and feces. Less than 5% of the daily dose is excreted unchanged in feces, 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 8 ml/min.

Linearity/Non-linearity:

Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7.5 mg and 15 mg following per oral or intramuscular administration.

Characteristics in patients

Hepatic/renal impairment:

Neither hepatic, mild to moderate nor renal insufficiency has a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded.

Geriatric population:

Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

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

Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. Toxicity studies in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits.

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). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. No evidence has been found of any mutagenic effect, either *in vitro* or *in vivo*. No carcinogenic risk has been found in the rat and mouse at doses far higher than those used clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Microcrystalline cellulose
Sodium citrate dihydrate
Polyvinyl pyrrolidone
Colloidal silicon dioxide
Crospovidone CL
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 25 °C.

6.5 Nature and contents of container
10 and 30 tablet blisters consisting of printed aluminum foil on one side and opaque PVDC on the other side.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)
206/18

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 20.07.2005
Date of last renewal :

10. DATE OF REVISION OF TEXT