PRODUCT MONOGRAPH

PrNU-MELOXICAM

Meloxicam

7.5 & 15.0 mg Tablets

Non-steroidal Anti-Inflammatory Drug (NSAID)

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Richmond Hill, Ontario
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Control#: 133151

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Pr **NU-MELOXICAM**
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 7.5 & 15 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Risk of Cardiovascular (CV) Adverse Events and Gastrointestinal (GI) Adverse Events.

NU-MELOXICAM (meloxicam) is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Randomized clinical trials with meloxicam have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing meloxicam. (see WARNINGS AND PRECAUTIONS – Cardiovascular).

Use of NSAIDS, such as meloxicam, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding) (see WARNINGS AND PRECAUTIONS).

The decision to prescribe NU-MELOXICAM should be based on the individual patient's overall risk (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first.

Use of NU-MELOXICAM should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events.

NU-MELOXICAM (meloxicam) tablets are indicated for:

- Symptomatic treatment of adult rheumatoid arthritis in adults and
- Painful osteoarthritis (arthrosis, degenerative joint disease) in adults

NU-MELOXICAM, as a NSAID, does NOT treat clinical disease or prevent its progression. NU-MELOXICAM, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (>65 years of age):
No data available.

Pediatrics (<18 years of age):
No data available.

CONTRAINDICATIONS

Coronary Artery Bypass Graft Surgery

NU-MELOXICAM (meloxicam) is CONTRAINDICATED for use post-coronary artery bypass surgery (CABG). Although NU-MELOXICAM has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.

Pregnancy, Breastfeeding

NU-MELOXICAM is CONTRAINDICATED for use during pregnancy. The risks during the third trimester are premature closure of the ductus arteriosus and prolonged parturition.

NU-MELOXICAM is CONTRAINDICATED for use in women who are breastfeeding because of the potential for serious adverse reactions in nursing infants. While no specific experience exists for NU-MELOXICAM, NSAIDS are known to pass into mother's milk.

See WARNINGS AND PRECAUTIONS – Pregnancy and Lactation

NU-MELOXICAM (meloxicam) should not be used in patients with known or suspected hypersensitivity to meloxicam or any other component of NU-MELOXICAM tablets. NU-MELOXICAM should not be used in patients in whom acute asthmatic attacks or symptoms of asthma, urticaria, nasal polyps, anaphylaxis, rhinitis, angioedema or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents since cross-sensitivity may exist. Fatal anaphylactoid reactions may occur in such individuals. Individuals with the above medical problem are at risk of a severe reaction even if they have

taken NSAIDs in the past without any adverse reaction. (see WARNINGS AND PRECAUTIONS – Anaphylactoid Reactions and Hypersensitivity Reactions).

NU-MELOXICAM is also contraindicated in:

- Significant liver impairment or active liver disease;
- Active gastric/duodenal/peptic ulcer, active GI bleeding;
- Recent cerebrovascular bleeding or other bleeding disorders;
- Severe uncontrolled heart failure;
- Inflammatory bowel disease;
- Severe renal impairment (creatinine clearance < 30 mL/min) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see WARNINGS AND PRECAUTIONS – Renal);
- Known hyperkalemia;
- Children and adolescents aged less than 18 years.

NU-MELOXICAM is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV).

Caution should be exercised in prescribing NU-MELOXICAM (meloxicam) to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as NU-MELOXICAM, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see WARNINGS AND PRECAUTIONS – Cardiovascular).

NU-MELOXICAM is a NSAID. Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Randomized clinical trials with meloxicam have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing NU-MELOXICAM. (see WARNINGS AND PRECAUTIONS – Cardiovascular).

Risk of Cardiovascular/Thromboembolic Events

Caution should be exercised in prescribing NU-MELOXICAM to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia/Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 1 mL/s (<60 mL/min)**

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration**. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Aseptic Meningitis

In rare cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Carcinogenesis and Mutagenesis

Meloxicam was not mutagenic in the Ames test, the host-mediated assay and a mammalian gene mutation assay (V79/HPRT), nor clastogenic in chromosome aberration assay in human lymphocytes and an in vivo micronucleus test in mouse bone marrow.

Carcinogenicity studies in rats and mice did not show any carcinogenic potential up to a dose level of 0.8 mg/kg in rats and 8 mg/kg in mice.

Cardiovascular (CV) Effects – Risk of Cardiovascular Events

NU-MELOXICAM is a NSAID. Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Randomized clinical trials with meloxicam have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing NU-MELOXICAM. (see WARNINGS AND PRECAUTIONS – Cardiovascular).

Use of NSAIDs, such as NU-MELOXICAM, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing NU-MELOXICAM should hypertension either develop or worsen with its use.

Use of NSAIDs, such as NU-MELOXICAM, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism.

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Fluid and Electrolyte Balance

Use of NSAIDs, such as NU-MELOXICAM, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing NU-MELOXICAM in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention.

Use of NSAIDs, such as NU-MELOXICAM can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporine, or some diuretics. Electrolytes should be monitored periodically.

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as peptic/duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms in patients treated with NU-MELOXICAM. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with NU-MELOXICAM, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population**. To minimize the potential risk for adverse GI events, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using NU-MELOXICAM and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing NU-MELOXICAM to patients with a prior history of peptic/duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agent (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Prospective, long-term studies required to compare the incidence of serious clinically significant upper gastrointestinal adverse events among patients taking meloxicam versus other NSAID products have not been performed.

For patients with a high risk of developing an adverse GI event, other management strategies that do NOT include the use of NSAIDS should be considered first.

There is no definitive evidence that the concomitant administration of histamine H_2 receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal adverse events or allow continuation of therapy when and if these adverse reactions appear (see DRUG INTERACTIONS).

Genitourinary

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment.

Should urinary symptoms occur, treatment with NU-MELOXICAM must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from hemophilia or platelet disorders should be carefully observed when NU-MELOXICAM is administered.

Anti-platelet Effects

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicyclic acid (ASA) their effect on platelet function is quantitatively less, or of shorter duration, and reversible. NU-MELOXICAM does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT).

NU-MELOXICAM and other NSAIDS have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for cardiovascular prophylaxis.

Concomitant administration of NU-MELOXICAM with low dose ASA increases the risk of GI ulceration and associated complications.

For information on interactions between low dose ASA and NU-MELOXICAM and any other interaction, see DRUG INTERACTIONS – Acetylsalicyclic Acid (ASA) or OTHER NSAIDs.

Anti-coagulants
Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of meloxicam with warfarin requires close monitoring of INR.

Even with therapeutic INR monitoring, increased bleeding may occur.

Blood dyscrasias
Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia, and agranulocytosis) associated with the use of nonsteroidal anti-inflammatory drugs are rare, but can occur with severe consequences.

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

The incidence of treatment-related anemia is more frequent than 1%. The incidence of disturbances of blood count, including differential white cell count, leukopenia and thrombocytopenia, is between 0.1 and 1%.

Hepatic/Biliary/Pancreatic
As with all NSAIDs, borderline elevations of one or more liver tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. 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 with other NSAIDs.

Patients with signs and/or symptoms 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 NU-MELOXICAM. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), NU-MELOXICAM should be discontinued.

If there is a need to prescribe NU-MELOXICAM in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions

Cross-sensitivity
Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs as well.

Anaphylactoid Reactions
As with other NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to meloxicam. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving meloxicam. NU-MELOXICAM should NOT be given to patients with the ASA-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 ASA or other NSAIDs (see CONTRAINDICATIONS). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

ASA-Intolerance
NU-MELOXICAM should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, Rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. As well, individuals with the above medical problems are at risk of a severe fatal reaction even if they have taken NSAIDs in the past without any adverse reaction (see CONTRAINDICATIONS).

Serious Skin Reactions
In rare cases, serious skin reactions such as Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Infection
NU-MELOXICAM, in common with other NSAIDs, meloxicam may mask the signs and symptoms of an underlying of infectious disease.

Neurologic (Central Nervous System)
Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of meloxicam. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of non-steroidal anti-inflammatory drugs. If such symptoms develop NU-MELOXICAM should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving NU-MELOXICAM for an extended period of time.

Peri-Operative Considerations
See CONTRAINDICATIONS, Coronary Artery Bypass Graft Surgery.

Pregnancy and Lactation
NU-MELOXICAM is contraindicated during pregnancy.

Inhibition of prostaglandin-synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation 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 increase 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.

During the third trimester of pregnancy all prostaglandin-synthesis inhibitors may expose the foetus 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;
- possible prolongation of bleeding time;
- inhibition of uterine contractions resulting in delayed or prolonged labour

NU-MELOXICAM is contraindicated for use in women who are breastfeeding because of the potential for serious adverse reactions in nursing infants. While no specific experience exists for NU-MELOXICAM, NSAIDS are known to pass into mother's milk.

See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, TOXICOLOGY.

Psychiatric
See WARNINGS AND PRECAUTIONS – Neurologic (Central Nervous System).

Renal
Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria, glomerulonephritis, renal medullary necrosis and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR<60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking diuretics and angiotensin converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporine and those that are the elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate an NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The extent to which metabolites may accumulate in patients with renal failure has not been studied with meloxicam. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Caution should be used when initiating treatment with NSAIDs in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy. Caution is also recommended in patients with pre-existing kidney disease. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 15 mL/min or 0.25 mL/sec). (see WARNINGS AND PRECAUTIONS – Renal)

NSAIDs can increase the risk of hyperkalemia (see WARNINGS AND PRECAUTIONS - Fluid and Electrolyte Balance).

Advanced Renal Disease: See CONTRAINDICATIONS.

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Concomitant Therapies

ASA (Acetylsalicylic Acid)

NU-MELOXICAM is NOT a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (See Drug Interactions – Drug-Drug Interaction-Acetylsalicylic Acid).

Corticosteroids

NU-MELOXICAM IS NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The pharmacological activity of meloxicam in reducing inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Sensitivity/Resistance (Cross-Sensitivity)

See WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions.

Sexual Function/Reproduction
The use of meloxicam, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

Skin
See WARNING AND PRECAUTIONS – Hypersensitivity Reactions: Serious Skin Reactions.

Special Populations

Pregnant Women
NU-MELOXICAM is contraindicated in pregnancy.

See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Pregnancy and Lactation, TOXICOLOGY.

Nursing Women
NU-MELOXICAM is contraindicated in nursing women.

See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Pregnancy and Lactation, TOXICOLOGY.

Pediatrics (<18 years of age): Safety and effectiveness of meloxicam in pediatric patients below the age of 18 years have not been evaluated.

Geriatrics (>65 years of age):
Patients older than 65 years (hereafter referred to as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs; the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population, older patients are also at risk of a lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a lower starting dose than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests
The following monitoring criteria and laboratory tests are recommended for patients taking meloxicam. This is not an exhaustive list.

Laboratory Testing:
- Potassium (Renal function, Hyperkalemia)
- INR/effects of anticoagulants (Co-prescription of oral anticoagulants)
- Serum transaminases and other liver function tests (liver function)
- Renal function parameters such as serum creatinine and serum urea (in case of Methotrexate, Diuretics, Cyclosporine, ACE-Inhibitor or ARB co-prescription, and in susceptible patients re: the renal effects of meloxicam, e.g. impaired renal function or dehydration)
- Lithium plasma concentrations (in case of Lithium co-prescription)

- Blood cell count, including differential white cell count (in case of Methotrexate co-prescription)

Monitoring Activities
- Patients with GI symptoms
- Patients with oral anticoagulation (see above)
- Blood pressure (in case of Antihypertensives co-prescription, and in susceptible patients with fluid retention)

For more information, please refer to the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The meloxicam phase 2/3 clinical trial database includes 12,722 patients treated with meloxicam 7.5 mg/day and 5,490 patients treated with meloxicam 15 mg/day. Meloxicam at these doses was administered to 980 patients for at least 6 months and to 533 patients for at least one year. Total exposure to meloxicam is 3,822 patient years with more than 850 patients treated for more than one year with once daily doses of up to 22.5 mg meloxicam. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across meloxicam trials.

A 12-week multicentre, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of meloxicam with placebo and with an active control. Table 1 depicts adverse events that occurred in $\geq$2% of the meloxicam treatment groups.

The adverse events that occurred with meloxicam in $\geq$ 2% of patients treated short-term (4-6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 2.

TABLE 1: ADVERSE EVENTS (%) OCCURRING IN ≥2% OF MELOXICAM PATIENTS IN A 12-WEEK OSTEOARTHRITIS PLACEBO AND ACTIVE-CONTROLLED TRIAL

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
No. of Patients	**157**	**154**	**156**	**153**
Gastrointestinal	17.2	20.1	17.3	28.1
Abdominal Pain	2.5	1.9	2.6	1.3
Diarrhea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	3.2	3.9	3.8	7.2
Body as a Whole				
Accident Household	1.9	4.5	3.2	2.6
Edema[1]	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-Like Symptoms	5.1	4.5	5.8	2.6
Central and Peripheral Nervous System				
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Respiratory				
Pharyngitis	1.3	0.6	3.2	1.3
Upper Respiratory Tract Infection	1.9	3.2	1.9	3.3
Skin				
Rash[2]	2.5	2.6	0.6	2

[1] WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined
[2] WHO preferred terms rash, rash erythematous and rash maculo-papular combined

TABLE 2: ADVERSE EVENTS (%) OCCURRING IN ≥ 2% OF MELOXICAM PATIENTS IN 4 TO 6 WEEKS AND 6 MONTH ACTIVE-CONTROLLED OSTEOARTHRITIS TRIALS

	4-6 Weeks Controlled Trials		6 Month Controlled Trials	
	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily
No. of Patients	**8955**	**256**	**169**	**306**
Gastrointestinal	11.8	18	26.6	24.2
Abdominal Pain	2.7	2.3	4.7	2.9
Constipation	0.8	1.2	1.8	2.6
Diarrhea	1.9	2.7	5.9	2.6
Dyspepsia	3.8	7.4	8.9	9.5
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.7	4.7	7.2
Vomiting	0.6	0.8	1.8	2.6
Body as a Whole				
Edema[1]	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
Central and Peripheral Nervous System				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
Hematologic				
Anemia	0.1	0	4.1	2.9
Musculo-Skeletal				
Arthralgia	0.5	0.0	5.3	1.3
Back Pain	0.5	0.4	3.0	0.7
Psychiatric				
Insomnia	0.4	0	3.6	1.6
Respiratory				
Coughing	0.2	0.8	2.4	1.0
Upper Respiratory Tract Infection	0.2	0.0	8.3	7.5
Skin				
Pruritis	0.4	1.2	2.4	0.0
Rash[2]	0.3	1.2	3.0	1.3
Urinary				
Micturition Frequency	0.1	0.4	2.4	1.3
Urinary Tract Infection	0.3	0.4	4.7	6.9

[1] WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined
[2] WHO preferred terms rash, rash erythematous and rash maculo-papular combined

Adverse event rates were similar in studies of Rheumatoid Arthritis. A 12-week double-blind placebo-controlled comparison to investigate meloxicam in the treatment of rheumatoid arthritis was conducted. Diclofenac 2 x 75 mg was included as active control to assess trial sensitivity. The adverse events rates reported in this trial are summarized by body system in Table 3.

TABLE 3: ADVERSE EVENTS REPORTED IN 12-WEEK DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL IN RHEUMATOID ARTHRITIS

	Meloxicam			Placebo	Diclofenac
	7.5 mg	15 mg	22.5 mg		2 x 75 mg
No. of subjects	**175**	**184**	**177**	**177**	**181**
Any AE [%]*	56	58	62	55	62
GI-AE [%]*	26	27	27	23	32
body as a whole [%]*	14	16	16	15	18
central & peripheral nervous system [%]*	15	10	13	15	14
musculoskeletal system [%]*	3	4	7	6	7
psychiatric [%]*	5	3	4	2	4
resistance mechanism [%]*	5	5	8	2	3
respiratory system [%]*	10	14	10	10	9
skin and appendages [%]*	9	11	5	7	8
urinary system [%]*	3	4	6	3	3

* % of patients treated is given; AE = adverse event; GI-AE = gastro-intestinal adverse event

A direct comparison of 22.5 mg/day to lower doses of meloxicam does not demonstrate any dose effect with regard to the incidence of gastro-intestinal adverse events, whereas a comparison of pooled data indicates that meloxicam 22.5 mg might be associated with a higher incidence of GI-AEs and also perforation, ulceration or bleeding from the upper gastro-intestinal tract (See CLINICAL TRIALS - Clinical Experience With Higher Than Recommended Doses (22.5 mg/day)). The maximum recommended dose of NU-MELOXICAM is 15 mg/day.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

The following is a list of adverse drug reactions regardless of causality occurring in < 2% of patients receiving meloxicam in clinical trials involving approximately 15,400 patients.

Body as a Whole: allergic reaction, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase.

Cardiovascular: angina pectoris, cardiac failure, hypertension (increase of blood pressure), hypotension, myocardial infarction, vasculitis, edema, flushes.

Heart Rate and Rhythm: arrhythmia, palpitation, tachycardia.

Central and Peripheral Nervous System: convulsions, paresthesia, tremor, vertigo, lightheadedness, headache, tinnitus, drowsiness.

Psychiatric Disorders: abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence.

Gastrointestinal: colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage (occult or macroscopic gastro-intestinal bleeding), hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, gastro-intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative, dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhea, transitory abnormalities of liver function parameters (e.g. raised transaminases or bilirubin), eructation, oesophagitis, gastroduodenal ulcer.

Gastro-intestinal bleeding, ulceration or perforation may potentially be fatal (See WARNINGS AND PRECAUTIONS – Gastrointestinal).

Hematologic: disturbances of blood count, including differential white cell count, leukopenia, purpura, thrombocytopenia and anemia. Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of a cytopenia.

Liver and Biliary System: ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis.

Metabolic and Nutritional: dehydration.

Respiratory: asthma, bronchospasm, dyspnea.

Skin and Appendages: alopecia, angioedema, bullous eruption, photosensitivity reaction (photosensitization), pruritus, skin rash, sweating increased, stomatitis, urticaria.

Special Senses: abnormal vision (including blurred vision), conjunctivitis, taste perversion, tinnitus.

Urinary System: albuminuria, abnormal renal function parameters (increased serum creatinine and/or serum urea), hematuria, acute renal failure.

Post-Market Adverse Drug Reactions

Post-market adverse drug reactions that are considered equivalent in quantity (frequency) and severity to events already identified in the Clinical Trial Database have not been re-listed in this section (see Clinical Trial Adverse Drug Reactions section). Adverse events which may be causally related to the administration of meloxicam that have come to light as a result of reports received in relation to administration of the marketed product are provided below. The incidence of these events is difficult to quantify.

Gastro-intestinal: hepatitis, gastritis;

Hematologic: agranulocytosis.

Liver and Biliary System: jaundice, liver failure.

Dermatological: bullous reactions, erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis.

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

Central Nervous System: confusion and disorientation, alteration of mood.

Genitourinary: acute renal failure, interstitial nephritis.

Vision Disorders: conjunctivitis, visual disturbances including blurred vision.

Hypersensitivity Reactions: angio-oedema and immediate hypersensitivity reactions, including anaphylactoid / anaphylactic reactions including shock.

DRUG INTERACTIONS

Overview

Meloxicam is eliminated almost entirely by hepatic metabolism, of which approximately two thirds are mediated by cytochrome (CYP) P450 enzymes (CYP 2C9 major pathway and CYP 3A4 minor pathway) and one-third by other pathways, such as peroxidase oxidation. The potential for a pharmacokinetic interaction should be taken into account when meloxicam and drugs known to inhibit, or to be metabolized by, CYP 2C9 and/or CYP 3A4 are administered concurrently.

Drug-Drug Interactions

Acetylsalicylic acid (ASA) or other NSAIDs:
Concomitant administration of aspirin (1000 mg TID) to healthy volunteers tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known; however, use of meloxicam in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effect is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for increased risk of gastro-intestinal ulcers and bleeding.

The exception is the use of low dose ASA for cardiovascular protection when another NSAID may be considered for an analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions. Concomitant administration of low-dose aspirin with NU-MELOXICAM may result in an increased rate of GI ulceration or other complications, compared to use of meloxicam alone. NU-MELOXICAM is not a substitute for aspirin for cardiovascular prophylaxis.

Some NSAIDs may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1. This potential interaction may exist when ibuprofen is taken prior to ASA dosing.

Anti-Platelet Agents (including ASA):
Oral anticoagulants, antiplatelet drugs, systemically administered heparin, thrombolytics: increased risk of bleeding, via inhibition of platelet function. If such co-prescribing cannot be avoided, close monitoring of the effects of anti-coagulants is required. See WARNINGS AND PRECAUTIONS, Hematologic section.

Anti-coagulants:
Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing NU-MELOXICAM therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding. The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering NU-MELOXICAM with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced.

Digoxin:

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after b-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Oral Hypoglycemics:
An interaction with oral hypoglycemic agents has been noted with some NSAIDs, however no interaction data is available for the co-administration of these agents with meloxicam.

Anti-Hypertensives:
NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, diuretics and NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

NSAIDs and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.

ACE Inhibitors:
Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.

Diuretics:
Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with furosemide and meloxicam, patients should be observed closely for signs of declining renal function (see WARNINGS AND PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

Glucocorticoids:
Glucocorticoids should be used with caution since they increase the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Food and Antacid Effects:
Drug intake after a high fat breakfast (75 g of fat) did not affect extent of absorption of meloxicam capsules, but led to 22% higher C_{max} values. Mean C_{max} values were achieved between five and six hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. NU-MELOXICAM (meloxicam) tablets can be administered without regard to timing of meals and antacids. (See ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics).

Methotrexate:
A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. In vitro, methotrexate did not displace meloxicam from its human serum binding sites.

In case combination treatment with methotrexate and NSAIDs 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 caused 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 drugs.

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.

Lithium:
In clinical trials, NSAIDs have produced a reduction in renal lithium clearance and an elevation of plasma lithium levels, which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg BID with meloxicam 15 mg QD as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by meloxicam. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.

Contraceptives:
No drug interaction information is available for meloxicam co-administered with oral contraceptive. A decrease of efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

Cholestyramine:
Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{1/2}$, from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine:
Concomitant administration of 200 mg cimetidine QID did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Cyclosporine:
Nephrotoxicity of cyclosporine may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment, renal function is to be measured.

Other Drug Interactions:
A population kinetics study with meloxicam indicated a lack of relevant interaction of sulfasalazine, gold compounds and glucocorticoids on the pharmacokinetics of meloxicam. No drug interaction data is available for meloxicam and the co-administration of the following products: phenytoin, acetaminophen, alcohol, aminoglycosides, butemide, colchicine, cyclosporin, indapamide, insulin, nephrotoxic agents, NSAIDs (other than ASA), oral contraceptives, potassium supplements, probenicid, valproic acid, zidovudine.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances, drowsiness or other central nervous system disturbances should refrain from these activities.

DOSAGE AND ADMINISTRATION

Dosing Considerations
In patients with increased risks of adverse reactions, treatment should be started at the dose of 7.5 mg once daily. In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg/day.

The maximum recommended daily dose of NU-MELOXICAM (meloxicam) tablets is 15 mg.

As dosage for use in children has yet to be established, usage should be restricted to adults.

Recommended Dose and Dosage Adjustment

Osteoarthritis: 7.5 mg once daily. If necessary, the dose may be increased to 15 mg once daily.

Rheumatoid arthritis: 15 mg once daily. According to the therapeutic response, the dose may be reduced to 7.5 mg once daily.

NU-MELOXICAM may be taken without regard to timing of meals.

No dose adjustment is necessary in patients with mild to moderate hepatic insufficiency.

No dose reduction is required in patients with clinically stable liver cirrhosis.

Missed Dose
If a dose is missed, the usual schedule must be resumed the following day. An extra dose must not be taken.

OVERDOSAGE

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose; all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

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. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm 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, or hemoperfusion may not be useful due to high protein binding.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic properties in animals. Meloxicam showed potent anti-inflammatory activity in all standard models of inflammation. NSAIDs are believed to exert their pharmacologic effects primarily through inhibition of the enzyme cyclooxygenase (COX). In turn, inhibition of this enzyme leads to an inhibition of biosynthesis of prostaglandins and other autacoids, substances which are potent biological mediators involved in diverse physiologic functions as well as pathologic conditions.

To date, two isozymes of COX have been identified and characterized, namely, COX-1 and COX-2 which have different intrinsic properties, expression controls and localization. COX-1 has been described as a constitutive enzyme occurring in many tissues including the gastrointestinal tract, kidney, lungs, brain and platelets. COX-1 is found in blood vessels, platelets, stomach and kidney. In contrast, COX-2, the inducible form, is mostly an inducible enzyme, limited in distribution and expressed in high levels in inflamed tissues. COX-2 is thought to be involved in inflammatory responses. Recent studies have shown that differential inhibition of these two isozymes is associated with a different biological profile. Meloxicam has shown a selective inhibition of COX-2 in several *in vitro* test systems, as demonstrated by a greater dose dependent inhibition of COX-2 over COX –1 at levels similar to those seen in plasma at therapeutic steady state concentrations. The prostaglandins produced by the cyclooxygenases are not the only factors involved in the protection of the gastric mucosa.

A human pharmacology study compared the effects of meloxicam 7.5 mg once daily and indomethacin 25 mg three times daily on platelet aggregation and platelet thromboxane formation, which are exclusively COX-1 dependent, and renal prostaglandin (PGE_2) excretion. Platelet aggregation and thromboxane formation were almost completely inhibited by indomethacin but remained unaffected by meloxicam. Meloxicam showed no significant effects on urinary PGE_2 excretion whereas indomethacin reduced urinary PGE_2 excretion by 43%.

In another study, meloxicam (7.5 and 15 mg) demonstrated a greater inhibition of COX-2 *ex vivo*, as demonstrated by a greater inhibition of lipopolysaccharide-stimulated PGE_2 production (COX-2) as compared with serum thromboxane production (COX-1).

Meloxicam has been shown to inhibit COX-2 in several *in vitro* and *ex vivo* test systems. The inhibition of thromboxane in platelets, and consequently platelet aggregation, occurs via inhibition of COX-1. Meloxicam inhibition of thromboxane in platelets (via COX-1) is dose dependent and incomplete at anti-inflammatory doses. No significant inhibition of platelet aggregation has been observed with meloxicam at the recommended therapeutic doses of 7.5 and 15 mg once daily.

Inhibition of COX-2 also inhibits the production of systemic prostacyclin. Inhibition of prostacyclin may have a pro-thrombotic effect.

Prospective, controlled, long-term (>3 months) studies required to establish the clinical significance of these results have not been performed.

Pharmacodynamics

See ACTION AND CLINICAL PHARMACOLOGY – Mechanism of Action.

Pharmacokinetics

Absorption: The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Meloxicam capsules have been shown to be bioequivalent to meloxicam tablets. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. The rate or extent of absorption was not affected by multiple dose administration, suggesting linear pharmacokinetics. With multiple dosing, steady state conditions were reached by day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting gastrointestinal recirculation.

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, respectively (C_{min} and C_{max} at steady state, respectively).

Continuous treatment for longer periods (e.g. six months) did not point to any changes in pharmacokinetics compared to steady state pharmacokinetics after two weeks of oral treatment with 15 mg meloxicam/day. Any differences after treatment longer than six months are thus rather unlikely.

TABLE 4 SINGLE DOSE AND STEADY STATE PHARMACOKINETIC PARAMETERS FOR ORAL 15 mg MELOXICAM (MEAN AND % CV)[1]

Pharmacokinetic Parameters (% CV)		Steady State						Single Dose			
		Healthy Male adults (Fed)[2]		Elderly males (Fed)[2]		Elderly females (Fed)[2]		Renal failure Fasted		Hepatic insufficiency (Fasted)	
		15 mg [3]		15 mg		15 mg		15 mg		15 mg	
N		24		5		8		12		12	
C_{max}	[μg/mL]	1.9	-25	2.3	-59	3.2	-24	0.59	-36	0.84	-29
t_{max}	[h]	6.5	-37	5	-12	6	-27	4	-65	10	-87
$t_{1/2}$	[h]	15	-45	21	-34	24	-34	18	-46	16	-29
CL/f	[mL/min]	8.3	-32	9.9	-76	5.1	-22	19	-43	11	-44
Vz/f[4]	[L]	10	-36	15	-42	10	-30	26	-44	14	-29

1) The parameter values in the Table are from various studies; 2)not under high fat conditions; 3) meloxicam tablets; 4) V z /f =Dose/(AUC•Kel)

Food and Antacid Effects: Drug intake after a high fat breakfast (75 g of fat) did not affect extent of absorption of meloxicam capsules, but led to 22% higher C_{max} values. Mean C_{max} values were achieved between five and six hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Meloxicam tablets can be administered without regard to timing of meals and antacids.

Distribution: The mean volume of distribution (Vss) of meloxicam is approximately 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 drug concentration, over the clinically relevant concentration range, but decreases to ~ 99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabelled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam.

Meloxicam concentrations in synovial fluid, after a single oral dose, 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. The significance of this penetration is unknown.

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 which is also excreted to a lesser extent (9% of dose). *In vitro* studies indicate that cytochrome P-450 2C9 plays an important role in this metabolic pathway with a minor contribution of the CYP 3A4 isozyme. Patients' 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 predominantly 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%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6% and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean elimination half-life ($t_{1/2}$) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 mL/min.

Special Populations and Conditions

Pediatric: In a study of 36 children, kinetic measurements were made in 18 children at doses of 0.25 mg/kg BW. Maximum plasma concentration C_{max} (-34%) as well as $AUC_{0-\infty}$ (-28%) tended to be lower in the younger age group (aged 2 to 6 years, n = 7) as compared to the older age group (7 to 14 years, n = 11) while weight normalized clearance appeared to be higher in the younger age group. A historical comparison with adults revealed that plasma concentrations were at least similar for older children and adults. Plasma elimination half-lives (13 h) were similar for both groups and tended to be shorter than in adults (15-20 h).

Geriatric: 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_{ss} and 32% higher $C_{max\ ss}$ as compared to younger females (< 55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

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

Gender: Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg meloxicam, the mean elimination half-life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs. 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C_{max} or T_{max} across genders.

Race: Pharmacokinetic data in Japanese subjects suggest a lower clearance of meloxicam in comparison to Caucasian subjects, but is not considered to require dose-adjustment due to the high intra-individual variability observed.

Hepatic Insufficiency: Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic insufficiency. 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: Meloxicam pharmacokinetics have been investigated in subjects with different degrees of renal insufficiency. Total drug plasma concentrations decreased with the degree of renal impairment while free AUC values were similar. Total clearance of meloxicam increased in these patients probably due to the increase in free fraction leading to an increased metabolic clearance. There is no need for dose adjustment in patients with mild to moderate renal failure (CrCL >15 mL/min or >0.25 mL/sec). Patients with severe renal insufficiency have not been adequately studied. The use of meloxicam in subjects with severe renal impairment is not recommended (see WARNINGS, Advanced Renal Disease).

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.

Hemodialysis: Following a single dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable.

STORAGE AND STABILITY

Store at controlled room temperature (15 – 30°C), safely out of the reach of children. Store in a dry place.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NU-MELOXICAM 7.5 mg Tablets: Each pastel yellow, round, biconvex tablet. Engraved “7.5” on one other. Available in bottles of 30 and 100 and blisters of 30.

NU-MELOXICAM 15 mg Tablets: Each pastel yellow, round, flat-faced, bevelled-edge tablet. Scored and engraved “MEL” over “15” on one side. Available in bottles of 30 and 100 and blisters of 30.

In addition to the active ingredient meloxicam, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, sodium bicarbonate, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

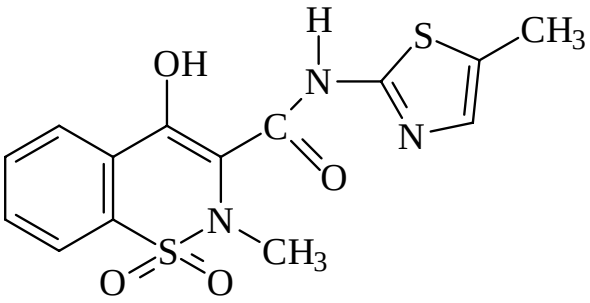
Drug Substance

Proper Name: Meloxicam

Chemical Name: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Molecular Formula and molecular mass: $C_{14}H_{13}N_3O_4S_2$; 351.4

Structural Formula:



Physicochemical properties: Meloxicam is a yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has pKa values of 1.1 and 4.2.

CLINICAL TRIALS

Randomized clinical trials with meloxicam have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Prospective, long-term studies required to compare the incidence of serious clinically significant upper gastrointestinal adverse events among patients taking meloxicam versus other NSAID products have not been performed.

Osteoarthritis

The use of meloxicam for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a double-blind controlled trial involving 464 patients treated with meloxicam for 12 weeks. Meloxicam (3.75 mg, 7.5 mg and 15 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and total WOMAC score (a self-administered questionnaire addressing pain, function and stiffness). Patients on meloxicam 7.5 mg daily and meloxicam 15 mg daily showed significant improvement in each of these endpoints compared with placebo.

The use of meloxicam for the management of signs and symptoms of osteoarthritis was evaluated in six additional double-blind, active-controlled trials in which a total of 9,589 patients were treated for 4 weeks to 6 months. In these trials, the efficacy of meloxicam, in doses of 7.5 and 15 mg/day, was comparable to piroxicam 20 mg/day and diclofenac SR 100 mg/day and consistent with the efficacy seen in the trial described above.

In two large (approximately 9,000 patients each), double-blind, active-controlled, 4-week, randomized trials, meloxicam 7.5 mg was compared to diclofenac SR 100 mg and piroxicam 20 mg. The risk of GI abnormalities in general, and dyspepsia and abdominal pain in particular, was significantly ($p<0.001$) less for meloxicam than for diclofenac (GI abnormalities 13.3% vs. 18.8%; dyspepsia 4.1% vs. 5.7%; abdominal pain 3.2 vs 5.6%) and for piroxicam (GI abnormalities 10.3% vs. 15.3%; dyspepsia 3.4% vs. 5.6%; abdominal pain 2.1% vs. 3.5%).

Rheumatoid Arthritis

In a double-blind, placebo-controlled study involving 466 patients with rheumatoid arthritis, once-a-day oral 7.5 mg or 15.0 mg doses of meloxicam over 3 weeks were significantly ($p<0.05$) superior to placebo in terms of disease activity assessed by both the patients and the investigators. Significant improvements were also seen for meloxicam compared to placebo in terms of duration of morning stiffness, swollen joint index, tender/painful joint index and performance of daily living activities.

In a 6-month, double-blind, multicentre study comparing 15 mg once daily oral dose of meloxicam (N=385), vs. 20 mg once daily piroxicam (N=193) in rheumatoid arthritis patients significant ($p<0.05$) improvements from baseline were observed in both groups. While global efficacy assessed by patients at the last visit appeared better ($p=0.003$) for piroxicam, there were no statistically significant differences between the groups with regard to 8 of 9 efficacy endpoints, including morning stiffness, pain in the morning and night, grip strength and Ritchie index. Significantly ($p<0.05$) fewer G.I. side effects were observed with meloxicam than with piroxicam.

Meloxicam, 7.5 mg once daily for 6 months, was compared with 750 mg Naproxen in patients with rheumatoid arthritis. There were no statistically significant differences between the two groups with regard to primary or 8 of 9 secondary efficacy endpoints. Decrease in hemoglobin was significantly ($p=0.025$) larger in the Naproxen than in the meloxicam group and patients on Naproxen also showed deterioration of renal function, where patients in the meloxicam group did not.

A 12-week double-blind placebo-controlled comparison to investigate doses of meloxicam 7.5 mg, 15 mg and 22.5 mg in the treatment of rheumatoid arthritis was also performed to investigate the full dose range of meloxicam in one trial. Diclofenac 2 x 75 mg was included as active control to assess trial sensitivity. Meloxicam 7.5 mg and 22.5 mg were statistically superior to placebo in all primary endpoints, whereas 15 mg was statistically superior in three out of five primary endpoints. Diclofenac was superior to placebo in four of the five primary endpoints. All active treatments were significantly superior to placebo in secondary endpoints such as withdrawal due to lack of efficacy, patient's and investigator's final global assessment of efficacy, the patient's assessment of status with regard to a change in the arthritic condition and after adjustment for baseline also for the modified health assessment questionnaire. Assessment of efficacy after 4 weeks revealed significant differences between the higher doses of meloxicam and placebo but not between 7.5 mg meloxicam and placebo thus indicating that 7.5 mg may be a valuable dose for the treatment of RA but that acute flares might require a higher starting dose.

Pooled Analysis

A pooled analysis was conducted of 15,071 patients treated with meloxicam at 7.5 mg - 30 mg per day in 35 clinical trials of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis. Trials were of 3 weeks to greater than one-year duration (most patients were enrolled in one-month studies). Almost all (99%) patients participated in trials that permitted enrollment of patients with a prior history of gastrointestinal perforation, ulcer or bleed. Approximately 39% of patients were at least 65 years of age. Results are shown in Table 5 (below). The incidence of upper gastro-intestinal perforation, ulcers, and bleeds reported in association with meloxicam is low. The pooled data including the 22.5 mg dose of meloxicam show that the incidence of serious upper gastro-intestinal events reported with meloxicam is dose dependent.

TABLE 5. CLINICALLY SIGNIFICANT UPPER GASTROINTESTINAL PERFORATION, OBSTRUCTION OR BLEED AMONG PATIENTS RECEIVING MELOXICAM IN A POOLED ANALYSIS OF 35 CLINICAL TRIALS

Daily Dose (mg/day)	Patients	Mean exposure (days)	Cases	Incidence
Meloxicam 7.5 mg/day	10,158	33	3	0.03%
Meloxicam 15 mg/day	2,960	179	9	0.30%
Meloxicam 22.5 mg/day	910	241	6	0.66%

Note that the maximum recommended dose for **meloxicam** is 15 mg/day.

Clinical Experience with Higher-than-recommended Doses (22.5 mg/day)

A direct comparison of meloxicam 22.5 mg to lower doses of meloxicam does not demonstrate any dose effect with regard to the incidence of gastro-intestinal adverse events. However, a comparison of pooled data indicates that meloxicam 22.5 mg might be associated with a higher incidence of gastro-intestinal adverse events and also perforation, ulceration or bleeding from the upper gastro-intestinal tract, as shown in Table 6. Pooled data indicate comparability of meloxicam 22.5 mg to piroxicam, naproxen and diclofenac in rheumatoid arthritis with regard to incidence of GI-AEs whereas the incidence of PUB appears to compare favourably with piroxicam and naproxen. The number of patients treated with diclofenac was insufficient to evaluate the incidence of perforation, ulceration or bleeding.

TABLE 6: PERCENTAGE OF PATIENTS WITH GASTROINTESTINAL ADVERSE EVENTS IN DOUBLE-BLIND TRIALS IN RHEUMATOID ARTHRITIS

	Meloxicam [mg]			Plac	Pir	Diclo	Nap
	7.5	**15**	**22.5**				
No. of Patients	747	1426	391	324	558	181	243
GI-AEs [%]	17.5	16.3	31	17.6	27.2	32	36.3
PUB* [%]	0.27	0.14	0.51	0	0.9	0	2.06

GI-AE = gastro-intestinal adverse event, * PUB = perforation, ulcer, bleed from the upper gastrointestinal tract, N = number of patients treated, n.a. = not applicable, plac = placebo, pir = piroxicam 20 mg, diclo = diclofenac 2 x 75 mg, nap = naproxen 750 mg and 1000 mg

Use with Acetylsalicylic Acid (ASA)

Use of concomitant low dose ASA was allowed in clinical trials with meloxicam. Overall, concomitant low dose ASA use was reported in 6.9% of patients, ranging from 4.3% to 8.0% for different treatment groups. The effect of low-dose ASA on the incidence of myocardial infarction was not investigated. The data show that the annualized incidence of thromboembolic events (myocardial infarction or embolic stroke) was similar for meloxicam (7.5 - 22.5 mg) compared to diclofenac 100 mg or piroxicam 20 mg.

Comparative Bioavailability Studies

Comparative bioavailability study was performed on healthy human volunteers under fasting conditions. The rate and extent of absorption of meloxicam was measured and compared following a single oral 15 mg dose of NU-MELOXICAM (meloxicam) or MOBICOX tablets. The results from measured data are summarized as follows:

Table 7: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Meloxicam (Dose: 1 x 15 mg) From Measured Data - Under Fasting Conditions Based on Meloxicam				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
	Nu-Meloxicam	Mobicox$^{TM/MC}$†		
AUC_T (ng.h/mL)	32492 33769 (31)	32654 33922 (31)	99.5	96.5 – 102.6
AUC_I (ng.h/mL)	35438 37532 (40)	36073 38573 (45)	98.2	94.7 – 101.9
C_{MAX} (ng/mL)	1159 1176 (17)	1175 1190 (17)	98.7	93.2 – 104.5
T_{MAX}^{*} (h)	5.70 (46)	5.20 (56)		
$T_{½}^{*}$ (h)	18.3 (31)	19.5 (40)		

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Mobicox$^{TM/MC}$ is marketed by Boehringer Ingelheim (Canada) Ltd.

DETAILED PHARMACOLOGY

See ACTION AND CLINICAL PHARMACOLOGY section.

TOXICOLOGY

Oral LD_{50} values ranged from about 98 mg/kg in female rats up to >800 mg/kg in minipigs. Intravenous values ranged from about 52 mg/kg in rats to 100 - 200 mg/kg in minipigs. Main signs of toxicity included reduced motor activity, anemia, and cyanosis. Most deaths occurred as a consequence of gastric ulcers and subsequent perforative peritonitis.

Repeated dose toxicity studies in rats and minipigs showed characteristic changes reported with other NSAIDs e.g. gastrointestinal ulceration and erosions and in the long term studies renal papillary necrosis. Gastrointestinal side effects were observed at oral doses of 1 mg/kg and higher in rats and of 3 mg/kg and above in minipigs. After intravenous administration doses of 0.4 mg/kg in rats and 9 mg/kg in minipigs caused gastrointestinal lesions. Renal papillary necrosis occurred only in rats at doses of 0.6 mg/kg or higher after lifetime exposure to meloxicam.

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. The affected dose levels exceeded the clinical dose (7.5-15 mg) by factor of 6.6 to 3.3-fold on a mg/kg dose basis (50 kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described.

Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits. Doses of 2.5 mg/kg in rats and 20 mg/kg and higher in rabbits were embryotoxic. Prolongation of gestation and labour and an increased incidence of stillbirths, which is a well-known phenomenon of prostaglandin inhibition, occurred in the peri- and postnatal study at doses of 0.125 mg/kg and above.

Meloxicam was not mutagenic in the Ames test, the host- mediated assay and a mammalian gene mutation assay (V79/HPRT), nor clastogenic in a chromosome aberration assay in human lymphocytes and an in vivo micronucleus test in mouse bone marrow.

Carcinogenicity studies in rats and mice did not show any carcinogenic potential up to a dose level of 0.8 mg/kg in rats and 8 mg/kg in mice.

In the above mentioned life-time studies in rats and mice meloxicam did not damage articular cartilage, it was considered to be chondroneutral in these species.

Meloxicam did not induce immunogenic reactions in tests on mice and guinea pigs. In several tests, meloxicam proved to be less phototoxic than some older NSAIDs but similar in this respect to both piroxicam and tenoxicam.

In local tolerance studies meloxicam was well tolerated by all tested routes of administration: intravenous, intramuscular, rectal, dermal, and ocular administration.

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PART III: CONSUMER INFORMATION

[Pr]NU-MELOXICAM
meloxicam

This leaflet is part III of a three-part "Product Monograph" published when NU-MELOXICAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NU-MELOXICAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NU-MELOXICAM (meloxicam) belongs to a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs) and is used to treat the symptoms of adult rheumatoid arthritis and painful osteoarthritis (arthrosis, degenerative joint disease) in adults.

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease or cardiovascular disease
- in people with risk factors for heart disease or cardiovascular disease

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleedings:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment for the shortest time needed

What it does:
NSAIDS do not cure arthritis, but they promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. NU-MELOXICAM will help you only as long as you continue to take it. It cannot prevent the disease from getting worse.

NU-MELOXICAM helps to relieve joint swelling, redness and pain of arthritis. Your body produces chemicals called prostaglandins. Some of these prostaglandins help line the stomach with a protective layer. In arthritis, other prostaglandins cause pain and swelling. At the dose prescribed by your doctor, NU-MELOXICAM reduces the type that causes pain and swelling.

What the medicinal ingredient is:
Meloxicam

What the important nonmedicinal ingredients are:
lactose monohydrate, microcrystalline cellulose, sodium bicarbonate, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide.

What dosage forms it comes in:
Tablets, 7.5 and 15 mg.

WHEN NOT TO USE THIS MEDICATION

WHEN SHOULD I NOT TAKE NU-MELOXICAM?
DO NOT TAKE NU-MELOXICAM if you have, or previously had:

- **Open Heart Surgery (planning to have or recently had)**

Or are:

- **Currently pregnant**
- **Currently Breastfeeding (or planning to breastfeed)**

In addition, DO NOT TAKE NU-MELOXICAM if you have, or previously had any of the following medical conditions;

- Known or suspected allergy to meloxicam or any other component of NU-MELOXICAM;
- Known or suspected allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs);
- Congestive heart failure;
- Ulcer;
- Bleeding from the stomach, gut or any other bleeding;
- Bleeding in the brain or other bleeding disorders;
- Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis);

- Liver Disease (active or severe);
- Kidney Disease (severe or worsening);
- High potassium in the blood.

NU-MELOXICAM is not recommended for use in patients under 18 years of age since safety and effectiveness have not been established.

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking NU-MELOXICAM unless directed to do so by your physician.

Patients who took a drug in the same class as NU-MELOXICAM after any type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lungs(s), and infections or other complication than those who did NOT take that drug.

It is not known whether long-term use of NU-MELOXICAM will increase the risk of heart attacks or strokes.

WARNINGS AND PRECAUTIONS

Before starting NU-MELOXICAM and to get the best possible treatment, be sure to tell your doctor if you:

- **Have angina;**
- **Have heart problems (e.g. congestive heart failure);**
- **Have had a heart attack, stroke or mini-stroke, loss of vision;**
- **Intend to become pregnant while taking this medication;**
- **Intend to breast feed while taking this medication;**

In addition, BEFORE TAKING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACISTS IF YOU:

- or a family member are allergic to or have had a reaction to NU-MELOXICAM or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, rofecoxib, tiaprofenic acid, tolmetin, nabumetone or tenoxicam, valdecoxib (NOT a complete list)). Allergic reactions may appear as increased sinus symptoms, hives (rash), new or worsened asthma or anaphylaxis (sudden collapse);
- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);
- have a history of stomach upset, ulcers, liver or kidney diseases;
- have blood or urine abnormalities;
- have high cholesterol;
- have high blood pressure;
- have atherosclerosis;
- have poor circulation to your extremities (hands and feet);
- have diabetes
- are a smoker or ex-smoker;
- are on any special diet, such as a low-sodium or low-sugar diet.
- Are taking any other medication (either prescription or non-prescription) including ASA or other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin, cholestyramine (NOT a complete list);
- Have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

While taking this medication:

- tell any other physician, dentist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- Do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- Your regular medical checkups are essential.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with NU-MELOXICAM include (NOT a complete list):

- ACE (Angiotensin Converting Enzyme) Inhibitors
  - e.g. enalapril, lisinopril, perindopril, ramipril
- Acetylsalicyclic Acid (ASA) or Other NSAIDs
  - e.g. ASA, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, Naproxen, celecoxib
- Anti-platelet agents
- Angiotensin receptor blockers (ARBs)
- Cholestyramine
- Corticosteroids (including Glucocorticoids)
  - e.g. prednisone
- Cyclosporine
- Diuretics

    - e.g. hydrochlorothiazide, furosemide
- Fluconazole
- Lithium
- Methotrexate
- Anticoagulants
    - e.g. warfarin
- Intrauterine Devices

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to help prevent heart and blood vessel disease while you are taking NU-MELOXICAM. Take only the amount of ASA prescribed by your healthcare provider. Taking NU-MELOXICAM and ASA has a greater potential to upset or damage your stomach than if you took NU-MELOXICAM alone.

PROPER USE OF THIS MEDICATION

Usual dose:
NU-MELOXICAM is intended for use in patients greater than 18 years of age for the shortest possible duration.

Medical Condition	Starting Dose	Maximum Dose (per day)
Symptomatic treatment of rheumatoid arthritis in adults	15 mg once daily. According to therapeutic response, the dose may be reduced to 7.5 mg once daily	15 mg once daily. In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg/day.
Painful osteoarthritis (arthrosis, degenerative joint in adults)	7.5 mg once daily. If necessary the dose may be increased to 15 mg once daily. In patients with increased risks of adverse reactions, treatment should be started at the dose of 7.5 mg once daily.	15 mg once daily. In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg/day

Take NU-MELOXICAM only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider ordered. You should take the lowest dose of this medication for the shortest time period.** Taking too much NU-MELOXICAM increases your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other disease or take other medications.

If you will be using NU-MELOXICAM for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seems to be similar to yours.

NU-MELOXICAM is NOT recommended for use in patients under 18 years of age since safety and effectiveness have NOT been established.

NU-MELOXICAM tablets may be taken with or without food.

Overdose:
If you take more than the prescribed dose, contact your health care provider immediately.

Missed Dose:
You should take NU-MELOXICAM as your doctor has prescribed. However, if you miss a dose, just resume your usual schedule the following day. Do not take an extra dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its beneficial effects, NU-MELOXICAM, like other NSAID drugs, may cause some undesirable reactions especially when used for a long time or in large doses. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur, they may require medical attention.

- Report all symptoms or side effects to your health care provider;

- NU-MELOXICAM may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking NU-MELOXICAM, do NOT drive or operate machinery;
- NU-MELOXICAM may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider;
- The use of meloxicam, as with any NSAID, may decrease fertility and is not recommended in women trying to get pregnant. Therefore, in women who have difficulties conceiving, stopping meloxicam should be considered.
- Check with your doctor if you are not getting any relief of your arthritis or if any problems develop.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor or pharmacist immediately**	**STOP taking NU-MELOXICAM and call your doctor or pharmacist immediately**
Bloody or black tarry stools		✳
Shortness of breath, wheezing, any trouble in breathing, or tightness in the chest		✳
Allergic reactions, such as: skin rash, hives or swelling, itching, chills, fever, muscle aches and pains, or other flu-like symptoms		✳
Yellow discolouration, the skin or eyes, with or without itchy skin		✳
Any change in the amount of colour of your urine (red or brown)		✳
Malaise, fatigue, loss of appetite		✳
Blurred vision, or any visual disturbance		✳
Headaches, stiff neck		✳
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea	✳	
Any pain or difficulty experienced while urinating	✳	
Swelling of the feet, lower legs, weight gain	✳	
Mental confusion, depression, dizziness, lightheadedness	✳	
Hearing problems	✳	

This is not a complete list of side effects. For any unexpected effects while taking NU-MELOXICAM, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15 – 30°C), safely out of the reach of children. Store in a dry place.

Do not keep outdated medicine or medicine no longer needed.

Keep out of reach of children.

This medication has been prescribed for your medical problem. Do not give it to anyone.

If you require more information on this drug, consult your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health product to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free to 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
    - **Fax toll-free to 1-866-678-6789, or**
    - **Mail to: Canada Vigilance Program**
      Health Canada
      Postal Locator 0701C
      Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you should require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Nu-Pharm Inc. at:

1-800-267-1438

This leaflet was prepared by Nu-Pharm Inc. Richmond Hill, Ontario L4B 1E4

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