PRODUCT MONOGRAPH

^{Pr}phl-MELOXICAM

(Meloxicam Tablets)

7.5 and 15.0 mg

Anti-inflammatory Analgesic Agent

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Control #: 088218

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory Analgesic Agent

ACTION AND CLINICAL PHARMACOLOGY

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. In contrast, COX-2 is mostly an inducible enzyme, limited in distribution and expressed in high levels in inflamed tissues. Recent studies have shown that differential inhibition of these two isozymes is associated with a different biological profile. The prostaglandins produced by the cyclooxygenases are not the only factors involved in the protection of the gastric mucosa.

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.

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.

Table 1: **Single Dose and Steady State Pharmacokinetic Parameters for Oral 15 mg Meloxicam (Mean and % CV)[1]**

		Steady State						Single Dose			
Pharmacokinetic Parameters (% CV)		**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
$T_{½}$	[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] Vz/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 radiolabeled 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

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 Cmax (-34%) as well as AUCO-∞ (-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.

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**).

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.

CLINICAL TRIALS

Bioequivalence Study

A single dose crossover comparative bioavailability study of phl-MELOXICAM 15 mg Tablets was performed under fasting conditions. Pharmacokinetic and bioavailability results are summarized in the following Table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

FOR SINGLE DOSE STUDIES

phl-MELOXICAM 15 mg Tablets, Pharmel Inc. Lot # Y21398

versus

MOBICOX 15 mg Tablets, Boehringer Ingelheim (Canada) Ltd., Lot # 003301

(A single 15 mg dose- 1 X 15 mg)

From measured data

uncorrected for potency

Geometric Mean

Arithmetic Mean (CV %)

PARAMETER	**Test** phl-Meloxicam Pharmel Inc. Canada	**Reference** Mobicox Boehringer Ingelheim Canada	% Ratio of Geometric Means	90% Confidence Interval	
				Lower	Upper
AUC_T (ng.h/m**L**)	35440.9 37236.1 (29.2)	33576.2 34929.1 (28.1)	105.55	100.60	110.75
AUC_I (**ng.h/mL**)	39636.4 42223.2 (34.5)	37939.3 40099.4 (33.8)	104.47	98.56	110.74
C_{MAX} (**ng/mL**)	1556.0 1584.2 (18.8)	1303.3 1328.0 (19.9)	119.39	110.96	128.47
T_{MAX}* (h)	3.50 (26.5)	4.45 (15.9)	---	---	---
$T_{½}$* (h)	20.96 (29.3)	21.19 (29.2)	---	---	---

*only the arithmetic mean is presented

Clinical Trials

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 9589 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 9000 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 to 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 2 (below). The incidence of upper gastrointestinal 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 2: 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 gastrointestinal adverse events. However, a comparison of pooled data indicates that meloxicam 22.5 mg might be associated with a higher incidence of gastrointestinal adverse events and also perforation, ulceration or bleeding from the upper gastrointestinal tract, as shown in Table 3. 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 3: 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 = Gastrointestinal 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.

INDICATIONS AND CLINICAL USE

phl-MELOXICAM (meloxicam) tablets are indicated for symptomatic treatment of

- rheumatoid arthritis
- painful osteoarthritis (arthrosis, degenerative joint disease) in adults.

CONTRAINDICATIONS

Known or suspected hypersensitivity to meloxicam or any other component of meloxicam tablets. Meloxicam tablets 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 have occurred in such individuals treated with other NSAIDs

(see **WARNINGS - Anaphylactoid Reactions** and **PRECAUTIONS - Hypersensitivity Reactions**).

Meloxicam is also contraindicated in: active peptic ulceration; severe hepatic insufficiency; non-dialysed severe renal insufficiency; children and adolescents aged less than 15 years; pregnancy or breast-feeding.

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

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe, and occasionally fatal, can occur at any time, with or without symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper GI problems, such as dyspepsia, are common, and may also occur at any time during NSAID therapy. Therefore, physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3 to 6 months, and in about 2 to 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. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to meloxicam (see **CLINICAL TRIALS**). Among 13,118 patients who have received meloxicam in clinical trials of 3 weeks to more than one-year duration at a daily dose of 7.5 mg to 15 mg, a total of twelve patients experienced a clinically significant upper GI event. Within 3 months, three patients on 7.5 mg (mean exposure 33 days) (0.03%) and within 6 months nine patients on 15 mg (mean exposure 179 days) (0.30%)

experienced an event. 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.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. 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 an adverse GI event, 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.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than ten-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding, such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to meloxicam 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 **CONTRAINDICATIONS** and **PRECAUTIONS - Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

In cases with advanced kidney disease, treatment with meloxicam is not recommended. If NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable (see **PRECAUTIONS** - **Renal Effects**).

Cross-sensitivity

Patients sensitive to any one of the non-steroidal anti-inflammatory drugs may be sensitive also to any of the other NSAIDs also.

Aseptic Meningitis

In occasional 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 erythematosis, mixed connective tissues diseases, etc.) seem to be predisposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Pregnancy

There are no studies with meloxicam in pregnant women. In late pregnancy, as with other NSAIDs, meloxicam should be avoided because it may cause premature closure of the ductus arteriosus. Meloxicam should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from meloxicam, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in children

Safety and effectiveness of meloxicam in pediatric patients below the age of 18 years have not been evaluated.

PRECAUTIONS

General

Meloxicam 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 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.

Gastrointestinal System

There is no definitive evidence that the concomitant administration of histamine H2 receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of therapy when and if these adverse reactions appear (see **Drug Interactions**).

Renal Function

Caution should be used when initiating treatment with meloxicam in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with meloxicam. Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS - Advanced Renal 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).

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. 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.

Genitourinary Tract

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 meloxicam must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic Function

As with all NSAIDs, borderline elevations of one or more liver tests 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 approximately1% 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 meloxicam. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), meloxicam should be discontinued.

Fluid and Electrolyte Balance

Fluid retention and edema have been observed in some patients taking NSAIDs, including meloxicam. Therefore, as with other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Meloxicam should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Hematology

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.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less or of shorter duration, and reversible. Meloxicam does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving meloxicam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

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.

Infection

In common with other anti-inflammatory drugs, meloxicam may mask the usual signs of infection.

Ophthalmology

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

Central Nervous System

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of anti-inflammatory drugs. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Hypersensitivity reactions

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 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, meloxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Information Physicians Should Provide to Patients

Meloxicam, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be made aware of the

importance of this follow-up (see **WARNINGS, Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding and Perforation**).

Patients should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see **WARNINGS**).

In late pregnancy, as with other NSAIDs, meloxicam should be avoided because it may cause premature closure of the ductus arteriosus.

Drug Interactions

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.

Aspirin

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, as with other NSAIDs, concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects. Concomitant administration of low-dose aspirin with meloxicam may result in an increased rate of GI ulceration or other complications, compared to use of meloxicam alone. Meloxicam is not a substitute for aspirin for cardiovascular prophylaxis.

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.

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.

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 **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

In clinical trials, NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. 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. Patients on lithium treatment should be closely monitored when meloxicam is introduced or withdrawn.

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.

Anticoagulants

Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing 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 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.

Oral Hypoglycemics

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

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.

Cytochrome P450 Interactions

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 metabolised by, CYP 2C9 and/or CYP 3A4 are administered concurrently.

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.

ADVERSE REACTIONS

The meloxicam phase 2/3 clinical trial database includes 12722 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 3822 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 multicenter, 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 4 depicts adverse events that occurred in $\geq$2% of the meloxicam treatment groups.

The adverse events that occurred with meloxicam in the ≥2% of patients treated short-term (4 to 6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 5.

Table 4: **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 & 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 5: Adverse Events (%) Occurring in a ≥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 7.5mg 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 & 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				
Insomia	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 6.

Table 6: 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 = gastrointestinal 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 gastrointestinal 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 gastrointestinal tract (See **ACTION AND CLINICAL PHARMACOLOGY - Clinical Data**). The maximum recommended dose of meloxicam is 15 mg/day.

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. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare (< 0. 1%).

Body as a Whole: allergic reaction, *anaphylactoid / anaphylactic reactions including shock*, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase.

Cardiovascular: angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis; **Heart Rate and Rhythm**: arrhythmia, palpitation, tachycardia.

Central and Peripheral Nervous System: convulsions, paresthesia, tremor, vertigo, *confusion and disorientation, alteration of mood*.

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, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative.

Hematologic: *agranulocytosis*, disturbances of blood count, including differential white cell count, leukopenia, purpura, thrombocytopenia. (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, *jaundice, liver failure*.

Metabolic and Nutritional: dehydration.

Respiratory: asthma, bronchospasm, dyspnea.

Skin and Appendages: alopecia, angioedema, bullous eruption, *erythema multiforme*, photosensitivity reaction, pruritus, *Stevens-Johnson syndrome*, sweating increased, *toxic epidermal necrolysis*, urticaria.

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

Urinary System: albuminuria, BUN increased, creatinine increased, hematuria, *interstitial nephritis,* acute renal failure.

SYMPTOMS AND TREATMENT OF OVERDOSE

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.

DOSAGE AND ADMINISTRATION

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.

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 phl-MELOXICAM tablets is 15 mg.

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

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

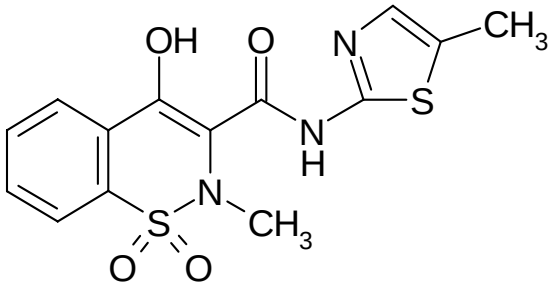
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Meloxicam

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

Structural Formula:



Molecular Formula: $C_{14}H_{13}N_3O_4S_2$

Molecular Weight: 351.41

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

Composition:

Each tablet contains 7.5 mg or 15 mg meloxicam

Excipients: Colloidal Silicone Dioxide, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, Starch, Sodium Citrate.

Stability and Storage Recommendations

Store at controlled room temperature (15^{o} to 30^{o}C), safely out of the reach of children. Store in a dry place.

AVAILABILITY OF DOSAGE FORMS

phl-MELOXICAM (meloxicam) Tablets, 7.5 mg and 15 mg

- Each yellow coloured, circular, flat, beveled uncoated tablet, with central break-line on one side and plain on the other, contains 7.5 mg meloxicam.
- Each yellow coloured, circular, flat, beveled uncoated tablet, with central break-line on one side and plain on the other, contains 15 mg meloxicam.
- Each of the above strengths is available in bottles of 100 and 500, and blister packs of 30 tablets.

INFORMATION FOR THE PATIENT

Please read this leaflet carefully before you use phl-MELOXICAM (meloxicam) tablets. It provides a summary of information that you should know about meloxicam, the active ingredient in phl-MELOXICAM tablets and how it should be used. If after reading this information you still have questions, please be sure to talk to your doctor or pharmacist.

WHAT is phl-MELOXICAM?

phl-MELOXICAM (meloxicam) belongs to a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs) and is used to treat the symptoms of certain types of arthritis. It 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, phl-MELOXICAM reduces the type that causes pain and swelling.

NSAIDS do not cure arthritis, but they promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. phl-MELOXICAM will help you only as long as you continue to take it.

You should take phl-MELOXICAM only as directed by your doctor. 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 doctor ordered. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to take phl-MELOXICAM regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication. Your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing unwanted effects.

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

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

- or a family member are allergic to or have had a reaction to phl-MELOXICAM or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of 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 blood pressure;
- have diabetes;
- have heart problems;
- are on any special diet, such as a low-sodium or low-sugar diet;
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding or intend to breast feed while taking this medication;
- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin;
- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

WHILE TAKING THIS MEDICATION:

- tell any other doctor, dentist or pharmacist that you consult or see, that your are taking this medication;
- some NSAIDs may cause drowsiness or fatigue in some people taking them. Do not drive or participate in activities that require alertness if you are drowsy, dizzy or light-headed after taking this medication;
- check with your doctor if you are not getting any relief of your arthritis or if any problems develop;
- report any untoward reactions to your doctor. This is very important as it will aid in the early

detection and prevention of potential complications;

- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;
- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;
- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;
- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;
- YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.

SIDE EFFECTS OF THIS MEDICATION

Along with its beneficial effects, phl-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.

CHECK WITH YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING ARE NOTED:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing, or tightness in the chest; skin rash, hives or swelling, itching;
- vomiting or persistent indigestion, nausea, stomach pain or diarrhea; yellow discoloration of the skin or eyes;
- any change in the amount or colour of your urine (red or brown); any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- blurred vision, or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;

- hearing problems.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

DOSING

phl-MELOXICAM should be taken once a day.

Your doctor will prescribe the dose of phl-MELOXICAM that is best suited for you. Always follow the directions your doctor has recommended. **It is important not to exceed the recommended daily dose**. phl-MELOXICAM tablets may be taken with or without food.

The recommended starting dose of phl-MELOXICAM in osteoarthritis is 7.5 mg once a day. The recommended starting dose of phl-MELOXICAM in rheumatoid arthritis is 15 mg once a day. Your doctor may adjust your dose depending on your response. The maximum recommended dose is 15 mg once a day.

WHAT TO DO IF YOU MISS A DOSE

You should take phl-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.

STORAGE

Store at room temperature (15^{o} to 30^{o}C). Store in a dry place.

phl-MELOXICAM IS NOT RECOMMENDED FOR USE IN PATIENTS UNDER 18 YEARS OF AGE SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICATION HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE

IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMAT1ON ON THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

phl-MELOXICAM Tablets contain 7.5 mg or 15 mg of Meloxicam, and the following non-medicinal ingredients (in alphabetical order): Colloidal Silicone Dioxide, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, Starch, Sodium Citrate.

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.

Cyclooxygenase (COX) exists in two isoforms, COX-1, the constitutive form and COX-2, the inducible form. COX-1 is found in blood vessels, platelets, stomach and kidney. COX-2 is thought to be involved in inflammatory responses. 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.

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. Meloxicain 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).

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 to 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.

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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