Pendaftar

PT. Boehringer Ingelheim Indonesia
Medical and Regulatory Affairs

LOCAL PRODUCT INFORMATION
No. 0203-11 **23 June 2014**

MOVI-COX®

Composition

1 tablet contains 7.5 mg or 15 mg

4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (= Meloxicam)

Excipients:
Tablets: sodium citrate, lactose, microcrystalline cellulose, polyvidone, colloidal silica, crospoly vidone, magnesium stearate

BADAN POM
ACC
Kategori : VaMa/VaMi-B
Perubahan/Penambahan:
Administratif;
Indikasi, farmakologi;
Keamanan; tdk perlu uji klinik
contraindication, special war
ning & precautions, interacti
fertility, pregnancy&lactatio
side effect, pharmacocine
- tics, toxicology
Va/18/21/14

Indications

MOVI-COX® is a non-steroidal anti-inflammatory drug indicated for
- Short term symptomatic treatment of acute exacerbations osteoarthritis
- Long term symptomatic treatment of rheumatoid arthritis (chronic poly arthritis)
- Symptomatic treatment of ankylosing spondylitis

Dosage and administration

Osteoarthritis: 7.5 mg/day. If necessary, the dose may be increased to 15 mg/day.

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

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Ankylosing spondylitis: 15 mg/day. According to the therapeutic response, the dose may be reduced to 7.5 mg/day.

In patients with increased risks of adverse reactions:
start treatment at the dose of 7.5 mg/day.

In dialysis patients with severe renal failure:
the dose should not exceed 7.5 mg/day.

As the potential for adverse reactions increases with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

Adolescents:
The maximum daily dose of meloxicam is 15 mg.

Tablets:

In general, usage should be restricted to ≥ 15 years (see section contraindications).
The total daily dose of tablets should be taken as a single dose and should be swallowed with water or other fluid in conjunction with food.

Combined administration of different dosage forms:
The total daily dosage of MOVI-COX® administered as tablets should not exceed 15 mg.

Contraindications

- Known hypersensitivity to meloxicam or any excipient of the product.
- There is a potential for cross sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs).
- Use in patients who have developed signs of asthma, nasal polyps, angio-oedema or urticaria following the administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs), because of a potential for cross- sensitivity .
- MOVI-COX® is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Active or recent gastro-intestinal ulceration / perforation.
- Active inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- *Severe hepatic insufficiency.*
- Non-dialysed severe renal insufficiency.
- Overt gastro-intestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- Severe uncontrolled heart failure.
- Pregnancy or breastfeeding.

BADAN POM
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Kategori : VaMa/VaMi-B
Perubahan/Penambahan:
Informasi Produk;
Penandaan;
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For the tablets the following contraindication applies in addition:
- In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to "Special warnings and precautions") the use of the product is contraindicated.

Special warnings and precautions

As with other NSAIDs gastro-intestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastro-intestinal events. The consequences of such events are generally more serious in the elderly.
Caution should be exercised when treating patients with a history of gastro-intestinal disease. Patients with gastro-intestinal symptoms should be monitored. MOVI-COX® should be withdrawn if gastro-intestinal ulceration or bleeding occurs.

RENEWAL

As with other NSAIDs caution should be exercised in patients receiving treatment with anticoagulants

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with

the use of MOVI-COX®. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. MOVI-COX® should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

NSAIDs inhibit the synthesis of renal prostaglandins, which play a supportive role in the maintenance of renal perfusion. In patients whose renal blood flow and blood volume are decreased, administration of an NSAID may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of non-steroidal anti-inflammatory therapy.
Patients at greatest risk of such a reaction are elderly individuals, dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those receiving a concomitant treatment with a diuretic, ACE inhibitor or angiotensin II receptor antagonist or those having undergone major surgical procedures, which led to hypovolaemia. In such patients the volume of diuresis and the renal function should be carefully monitored at the beginning of therapy.
In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.
The dose of MOVI-COX® in patients with end-stage renal failure on haemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 ml/min).

As with other NSAIDs, occasional elevations of serum transaminases or other parameters of liver function have been reported. In most cases these have been small and transient increases above the normal range. If the abnormality is significant or persistent, MOVI-COX® should be stopped and follow up tests carried out.
No dose reduction is required in patients with clinically stable liver cirrhosis.

Frail or debilitated patients may tolerate side effects less well and such patients should be carefully supervised. 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.

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended.

RENEWAL

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

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.

BADAN POM
ACC
Perubahan/Penambahan;
Administratif;
18/01/16

For relevant drug interactions that require particular attention, see section "Interactions".

Tablets:

MOVI-COX® tablets 7.5 mg contains 47 mg lactose per maximum recommended daily dose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia should not take this medicine.
MOVI-COX® tablets 15 mg contains 20 mg lactose per maximum recommended daily dose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia should not take this medicine.

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).
- MOVICOX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs can cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

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

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
NSAIDs, including MOVI-COX®, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including MOVI-COX®, should be used with

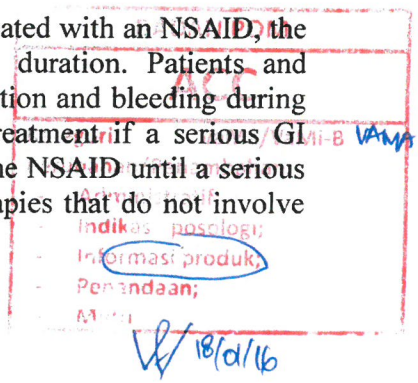
caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. MOVI-COX® should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including MOVI-COX®, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, 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.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. 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 in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.



Interactions

- Other Prostaglandin Synthetase Inhibitors (PSI) including glucocorticoids and salicylates (acetylsalicylic acid): Co-administration of PSIs may increase the risk of gastro-intestinal ulcers and bleeding, via a synergistic effect, and is not recommended. The concomitant use of meloxicam with other NSAIDs is not recommended. 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.
- Oral anticoagulants , antiplatelet drugs, systemically administered heparin, thrombolytics and Selective Serotonin Reuptake Inhibitors (SSRIs) increased risk of bleeding, via inhibition of platelet function.

- Lithium: NSAIDs have been reported to increase lithium plasma levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.
- Methotrexate: NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended. The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity. Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.
- Contraception: A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.
- Diuretics: Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving MOVI-COX® and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.
- Antihypertensives (e.g. beta-blockers, ACE-inhibitors, vasodilators, diuretics): A reduced effect of the antihypertensive drug by inhibition of vasodilating prostaglandins has been reported during treatment with NSAIDs.
- NSAIDs and angiotensin-II receptor antagonists as well as 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.
- Cholestyramine binds meloxicam in the gastro-intestinal tract leading to a faster elimination of meloxicam .
- Nephrotoxicity of cyclosporine may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured.
- Pemetrexed: For the concomitant use of meloxicam with pemetrexed in patients with creatinine clearance from 45 to 79 ml/min, the administration of meloxicam should be paused for 5 days before, on the day of, and 2 days following pemetrexed administration. If a combination of meloxicam with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastro-intestinal adverse reactions. In patients with creatinine clearance below 45 ml/min the concomitant administration of meloxicam with pemetrexed is not recommended

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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. Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these drugs and meloxicam. Patients concomitantly using meloxicam with sulfonylureas or nateglinide should be carefully monitored for hypoglycemia

VAMA

Perubahan/Penambahan:
Administratif;
Indikasi; posologi;
Produk;
Penandaan;

18/01/16

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

Fertility, pregnancy and lactation

MOVI-COX® 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 and gastrochisis 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 preclinical studies, 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 preclinical studies given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy all prostaglandin-synthesis inhibitors may expose the foetus to:

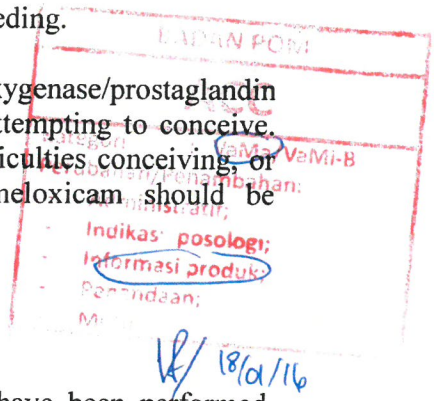
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour.

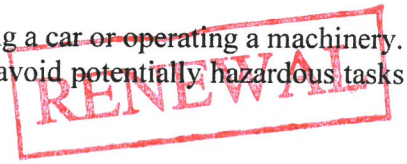
While no specific experience exists for MOVI-COX® in humans, NSAIDs are known to pass into mother's milk.
Administration therefore is contraindicated in women who are breastfeeding.

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. Meloxicam may delay ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.



Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects like visual disturbance including blurred vision, dizziness, somnolence, vertigo and other central nervous system disturbances.
Therefore, caution should be recommended when driving a car or operating a machinery.
If patients experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery.



Side effects

Clinical trial and epidemiological data suggest that use of some NSAID s (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleedings, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in 27 clinical trials with a treatment duration of at least 14 days. The information is based on clinical trials involving 15197 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to one year.
Adverse drug reactions that have come to light as a result of reports received in relation to administration of the marketed product are included.

Adverse reactions have been ranked under headings of frequency using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (1/10,000), not known (can not be estimated from the available data)

Blood and lymphatic system disorders
Uncommon: Anaemia
Rare: Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia,
Very rare cases of agranulocytosis have been reported

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

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

Nervous system disorders
Common: Headache
Uncommon: Dizziness, somnolence

Eye disorders
Rare: Visual disturbance including vision blurred, conjunctivitis

Ear and labyrinth disorders
Uncommon: Vertigo
Rare: Tinnitus

BADAN POM
ACC
Kategori : VaMa/VaMi-B
Perubahan/Penambahan:
- Administratif;
- Indikasi, posologi;
- Informasi produk;
- Pemberian;
- Lain-lain
18/01/14

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

Vascular disorders
Uncommon: Blood pressure increased, flushing

Respiratory, thoracic and mediastinal disorders
Rare: Asthma in individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders
Very common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea
Uncommon: Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation.
Rare: Colitis, gastroduodenal ulcer, oesophagitis.
Very rare: Gastrointestinal perforation, gastrointestinal haemorrhage, ulceration or perforation may sometimes be severe potentially be fatal, especially elderly.

Hepatobiliary disorders
Uncommon: Liver function test abnormal (e.g. raised transaminases or bilirubin)
Very rare: Hepatitis

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

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

Reproductive System and Breast Disorders
infertility female, ovulation delayed .

General disorders and administration site conditions
Uncommon: Oedema including oedema of the lower limbs

BADAN POM
ACC
VaMa/VaMi-6
Perubahan/Penambahan:
- Administratif;
- Indikasi, posologi;
- Informasi produk;
- Penandaan;
18/01/16

RENEWAL

Overdose

Tablets
In case of overdose the standard measures of gastric evacuation and general supportive measures should be used, as there is no known antidote. It has been shown in a clinical trial that cholestyramine accelerates the elimination of meloxicam.

Pharmacological properties

MOVI-COX® is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties in animals. Meloxicam showed potent anti-inflammatory activity in all standard models of inflammation. A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

Comparison of the ulcerogenic dose and the anti-inflammatory effective dose in the rat adjuvant arthritis model confirmed a superior therapeutic margin in animals over standard NSAIDs. In vivo, meloxicam inhibited prostaglandin biosynthesis more potently at the site of inflammation than in the gastric mucosa or the kidney.

These differences are thought to be related to a selective inhibition of COX-2 relative to COX-1 and it is believed that COX-2 inhibition provides the therapeutic effects of NSAIDs whereas inhibition of constitutive COX-1 may be responsible for gastric and renal side effects.

The COX-2 selectivity of meloxicam has been confirmed both in vitro and ex vivo in a number of test systems. In the human whole blood assay, meloxicam has been shown in vitro to inhibit COX-2 selectively. 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 thromboxane production in clotting blood (COX-1). These effects were dose-dependent. Meloxicam has been demonstrated to have no effect on either platelet aggregation or bleeding time at recommended doses ex vivo, while indomethacin, diclofenac, ibuprofen and naproxen significantly inhibited platelet aggregation and prolonged bleeding.

In clinical trials, gastro-intestinal adverse events overall were reported less frequently with meloxicam 7.5 mg and 15 mg than with the NSAIDs with which it has been compared, due predominantly to a lower reporting incidence of events such as dyspepsia, vomiting, nausea and abdominal pain. The incidence of upper gastro-intestinal perforation, ulcers, and bleeds reported in association with meloxicam is low and dose dependent.

There is no single study powered adequately to detect statistically differences in the incidence of clinically significant upper gastro-intestinal perforation, obstruction, or bleeds between meloxicam and other NSAIDs. A pooled analysis has been conducted involving patients treated with meloxicam in 35 clinical trials in the indications osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis [85]. Exposure to meloxicam in these trials ranged from 3 weeks to one year (most patients were enrolled in one-month studies). Almost all patients participated in trials that permitted enrolment of patients with a prior history of gastro-intestinal perforation, ulcer or bleed.

The incidence of clinically significant upper gastro-intestinal perforation, obstruction, or bleed (POB) was assessed retrospectively following independent blinded review of cases. Results are shown in the following table.

RENEWAL

BADAN POM
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Penambahan:
Administratif;
Indikasi, posologi;
Informasi produk;
Penandaan;
18/01/16

Cumulative risk of POBs for meloxicam 7.5 mg and 15 mg from BI clinical trials compared to diclofenac and piroxicam (Kaplan-Meier estimates)

TREATMENT Daily dose	Interval (days)	Patients at interval midpoint	POBs within interval	Risk (%)	95% confidence interval
Meloxicam					
7.5 mg	1 - <30	9636	2	0.02	0.00 – 0.05
	30 - <91	551	1	0.05	0.00 – 0.13
15 mg	1 - <30	2785	3	0.12	0.00 – 0.25
	30 - <91	1683	5	0.40	0.12 – 0.69
	91 - <182	1090	1	0.50	0.16 – 0.83
	182 - <365	642	0	0.50	
Diclofenac 100 mg	1 - <30	5110	7	0.14	0.04 – 0.24
	30 - <91	493	2	0.55	0.00 – 1.13
Piroxicam 20 mg	1 - <30	5071	10	0.20	0.07 – 0.32
	30 - <91	532	6	1.11	0.35 – 1.86

Pharmacokinetics

Absorption

Oral administration:
Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration.
Following single dose administration of meloxicam, median maximum plasma concentrations are achieved within 5-6 hours with solid oral dosage forms (tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days.
Once daily dosing leads to mean 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, correspondingly).

Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours.

Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids. Dose linearity was demonstrated after oral administration in the therapeutic dose range of 7.5 to 15 mg.

Distribution
Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%).
Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma.

RENEWAL

BADAN POM
VaMi/VaMi-B
Penambahan;
Aktif;
Posologi;
Jenis produk;
Kemasan;
18/01/16

Volume of distribution is low, i.e. approx. 11 L after i.m. or i.v. administration, and shows interindividual variation in the order of 7 - 20%.
The volume of distribution following administration of mulitple oral doses of meloxicam (7.5 to 15 mg) is about 14-17 L with coefficients of variation ranging from *24 %* to 32%.

Biotransformation
Meloxicam undergoes extensive hepatic biotransformation.
Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive.
The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'- hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.
The mean elimination half-life varies between 13 and 25 hours after oral, i.m. and i.v. administration.
Total plasma clearance amounts about 7 - 12 mL/min following single doses orally, intravenously or rectally administered.

Linearity/ non-linearity
Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7.5 mg to 15 mg following per oral or intramascular administration.

Special populations
Patients with hepatic/renal insufficiency
Neither hepatic insufficiency nor mild renal insufficiency has a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significantly higher total drug clearance. A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations.

Elderly
Elderly male subjects exhibited similar mean pharmacokinetic parameters but the elimination half-lifes is significantly longer compared to those of young male subjects. Elderly female patients showed higher AUC-values and longer elimination half-lives compared to those of younger subjects of both genders. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

RENEWAL

Children
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 normalised clearance appeared to be higher in the younger age group. A historical comparison with adults revealed that plasma

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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).

Toxicology

An extensive toxicological program confirmed that meloxicam has an acceptable safety profile.
Oral LD50 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, anaemia, and cyanosis. Most deaths occurred as a consequence of gastric ulcers and subsequent perforation leading to peritonitis.

Repeat dose toxicity studies in rats and minipigs showed characteristic changes reported with other NSAIDs e.g. gastro-intestinal ulceration and erosions, and in the long term studies, renal papillary necrosis. Gastro-intestinal side effects were observed at oral doses of 1mg/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 gastro-intestinal 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. 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 a factor of 10 to 5-fold on an mg/kg dose basis (75 kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. Nonclinical studies indicate that meloxicam can be found in the milk of nursing rats.

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

Carcinogenicity studies in rats and mice did not show a carcinogenic potential up to dose levels of 0.8 mg/kg in rats and 8 mg/kg in mice [142,143]. In these studies meloxicam was chondro-neutral, i.e. it did not damage the articular cartilage following long-term exposure.

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

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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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Remarks : ***Black*** *(Current CCDS 0203-10);* ***Green*** *(Proposed as update safety claim CCDS 0203-11)*

Availability

Tablet 7.5 mg Reg. No. DKL0133701110A1
Box contains 3 strips of 10 tablets

Tablet 15 mg Reg. No. DKL0133701110B1
Box contains 3 strips of 10 tablets

Only on doctor's prescription.
Hanya dengan resep dokter.

Store below 30 °C.
Store in a safe place, out of reach of children.

Manufactured by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Under license from:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

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