

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1103/001/001

Case No: 2034435

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

F.A.L. Duiven BV

Nieuwgraaf 93, NL-6920 AB Duiven, Netherlands

an authorisation, subject to the provisions of the said Regulations, in respect of the product

MELOXICAM FAL 7.5mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/07/2007** until **16/02/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Meloxicam FAL 7.5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.5 mg meloxicam.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Light yellow, round, flat tablets, scored on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Exacerbations of osteoarthritis: 7.5 mg/day (one tablet of 7.5 mg or half a 15 mg tablet).

If necessary, in the absence of improvement, the dose may be increased to 15 mg/day (two tablets of 7.5 mg or one tablet of 15 mg).

Rheumatoid arthritis, ankylosing spondylitis: 15 mg/day (two tablets of 7.5 mg or one tablet of 15 mg). (see also special populations).

According to the therapeutic response, the dose may be reduced to 7.5 mg/day (one tablet of 7.5 mg tablet or half a 15 mg tablet).

DO NOT EXCEED THE DOSE OF 15 mg/day.

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

Special populations

Elderly patients and patients with increased risks for adverse reaction (see section 5.2): The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day (see section 4.4).

Renal impairment (see section 5.2)

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

No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see section 4.3).

Hepatic impairment

No dose reduction is required in patients with mild to moderate hepatic impairment (For patients with severely impaired liver function, see section 4.3).

Children

Meloxicam should not be used in children aged under 15 years.

Meloxicam exists in other dosages or pharmaceutical forms which may be more appropriate.

4.3 Contraindications

- Hypersensitivity to meloxicam or to one of the excipients. The possibility exists of crossover sensitivity with aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Meloxicam FAL, tablets should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or NSAIDs.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure.
- Non-dialyzed severe renal failure.
- Children aged under 15.
- Pregnancy (see Pregnancy and lactation).
- Lactation.
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders.
- Severe uncontrolled heart failure.

4.4 Special warnings and precautions for use

The use of Meloxicam FAL with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see sections 4.2, and GI and cardiovascular risks below).

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2).

Gastrointestinal bleeding, ulceration and perforation: Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin or other drugs likely to increase gastrointestinal risk (See below and 4.5).

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5).

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (See section 4.8 – undesirable effects).

If gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, the drug should be withdrawn.

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 NSAIDs (see section 4.8). 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. Meloxicam FAL should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

As with most NSAIDs, temporary increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory disturbances have occasionally been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken.

Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and edema have been reported in association with NSAID therapy.

Clinical and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam.

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

NSAIDs inhibit the synthesis of renal prostaglandins involved in the maintenance of renal perfusion in patients with decreased renal blood flow and blood volume. Administration of NSAIDs in such situations may result in the decompensation of latent renal failure.

However, renal function returns to its initial status when treatment is withdrawn. This risk concerns all elderly individuals, patients with congestive heart failure, cirrhosis of the liver, nephrotic syndrome or renal failure as well as patients on diuretics, intestinal epithelial cell antibodies (IECAs) or having undergone major surgery leading to hypovolaemia. Careful monitoring of urine output and renal function during treatment is necessary in such patients (see sections 4.2 and 4.3).

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

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

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 syntheses, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

Meloxicam should not be used in children aged under 15 years.

Caution is required if meloxicam is administered to patients suffering from, or with a previous history of, bronchial asthma since there is a possibility that NSAIDs could cause bronchospasm in such patients.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The use of meloxicam may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Meloxicam should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions

Other NSAIDs, including salicylates (acetylsalicylic acid):

Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended (see section 4.4).

Diuretics:

Treatment with NSAIDs is associated with potential for acute renal failure, notably in dehydrated patients. Patients receiving meloxicam and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment (see section 4.4).

Anticoagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Thrombolytics and anti platelet drugs:

Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa (see section 4.4).

Selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding (see section 4.4).

ACE inhibitors and angiotensin II receptor antagonists:

NSAIDs (including acetylsalicylic acid at doses > 3g/d) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration, which may be exacerbated when renal function is altered. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking meloxicam concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Other antihypertensive drugs (e.g. Beta-blockers):

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

Cyclosporins:

Nephrotoxicity of cyclosporine may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

Corticosteroids:

Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Intrauterine devices:

NSAIDs have been reported to decrease the efficacy of intrauterine devices.

A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further

confirmation.

Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs)

Lithium:

NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.

Methotrexate:

NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended (see section 4.4).

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 (see above). (See section 4.8).

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)

Cholestyramine:

Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50 % and the half-life decreases to 13 ± 3 hrs. This interaction is of clinical significance.

CYP3A4 and CYP2C9 inhibitors, inducers and substrates:

Possible metabolic interactions.

No clinically relevant pharmacokinetic drug-drug interactions were detected with respect of the concomitant administration of antacids, cimetidine and digoxin, but increased serum levels of digoxin may occur.

4.6 Pregnancy and lactation

Pregnancy

In animals, lethal effects on the embryo have been reported at doses far higher than those used clinically.

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

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

Thus all NSAIDs are absolutely contraindicated during the final three months.

Lactation

It is unknown whether meloxicam passes into mother's milk. Meloxicam should not be given to nursing mothers.

4.7 Effects on ability to drive and use machines

There are no specific studies about such effects. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on these abilities.

However, when adverse effects such as vertigo or drowsiness occur it is advisable to refrain from these activities.

4.8 Undesirable effects

a) General description

The following adverse effects, which may be causally related to the administration of meloxicam, have been reported. The frequencies given below are based on corresponding occurrences in clinical trials, regardless of any causal relationship. The information is based on clinical trials involving 3750 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 18 months (mean duration of treatment 127 days).

Adverse events which may be causally related to the administration of meloxicam that have come to light as a result of reports received in relation to the administration of the marketed product are included.

Adverse reactions have been ranked under the headings of frequency using the following convention:

Very common (= 1/10); common (= 1/100, <1/10); uncommon (=1/1,000, <1/100); rare (= 1/10,000, <1/1000); very rare (<1/10,000)

b) Table of adverse reactions

Blood and the lymphatic system disorders

Common: Anaemia.

Uncommon: Disturbances of blood count; leucocytopenia; thrombocytopenia; agranulocytosis (see section c.).

Immune system disorders

Rare: Anaphylactic/anaphylactoid reactions.

Psychiatric disorders

Rare: Mood disorders, insomnia and nightmares.

Nervous system disorders

Common: Light-headedness, headache.

Uncommon: Vertigo, tinnitus, drowsiness.

Rare: Confusion.

Eye disorders

Rare: Visual disturbances including blurred vision.

Cardiac disorders

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

Clinical and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Uncommon: Palpitations

Vascular disorders

Uncommon: Increase in blood pressure (see section 4.4), flushes.

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (See section 4.4). Nausea, vomiting, diarrhoea,

flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Common: Dyspepsia, nausea and vomiting symptoms, abdominal pain, constipation, flatulence, diarrhoea.
 Uncommon: Gastrointestinal bleeding, peptic ulcers, eosophagitis, stomatitis.
 Rare: Gastrointestinal perforation, gastritis, colitis.

The peptic ulcers, perforation or gastrointestinal bleeding, that may occur can be sometimes severe, especially in elderly (see section 4.4).

Hepato-biliary disorders

Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin).
 Rare: Hepatitis.

Skin and subcutaneous tissue disorders

Common: Pruritis, rash.
 Uncommon: Urticaria.
 Rare: angioedema, such as erythema multiforme, photosensitivity reactions.
 Very rare: bullous reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Renal and urinary disorders

Uncommon: Disturbances of laboratory tests investigating renal function (e.g. raised creatinine or urea).
 Rare: Renal failure (see section 4.4).

c) Information Characterising Individual Serious and/or Frequently Occurring Adverse Reactions

Isolated cases of agranulocytosis have been reported in patients treated with meloxicam and other potentially myelotoxic drugs (see section 4.5).

4.9 Overdose

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. 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. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

Severe gastrointestinal lesions may be treated with antacids and H₂ receptor antagonists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drug, ATC Code: M01AC06.

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

The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However there is at least one common mode of action shared by all NSAIDs (including meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

5.2 Pharmacokinetic properties

The bioavailability of meloxicam following oral administration is on the average 89 %.

Absorption:

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

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4-1.0 µg/mL for 7.5 mg doses and 0.8-2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively.

Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

Distribution:

Meloxicam is very strongly bound to plasma proteins, essentially albumin (90 %). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11 L. Interindividual variation is the order of 30-40 %.

Biotransformation:

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

Elimination:

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

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

Linearity/non-linearity:

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

Special populations

Hepatic/renal Insufficiency:

Neither, mild nor moderate hepatic or renal insufficiencies have a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded in dialysed severe renal failure (see section 4.2).

Meloxicam is contraindicated in severe hepatic insufficiency and non-dialysed severe renal failure (see section 4.3).

Elderly:

Mean plasma clearance at steady state.

5.3 Preclinical safety data

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

Non-toxic doses were 3 to 10 times higher than clinically used doses, according to animal species used.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Lactose monohydrate
Microcrystalline cellulose
Povidone
Crospovidone
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Alu/PVC/PVDC-blisters containing 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

F.A.L. Duiven BV
Nieuwgraaf 93
NL-6920 AB Duiven
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 1103/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 17 February 2006

10 DATE OF REVISION OF THE TEXT

July 2007