SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Meloxicam 15 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg meloxicam

Excipients of known effect:
Each tablet contains 86 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Yellow, round, flat, uncoated tablet with bevelled edge. Scored from one side, flat from the other side.

The score line is not intended for breaking the tablet.

4.1 Therapeutic indications

Short-term symptomatic treatment of acute flare-ups of osteoarthrosis.
Long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.
Meloxicam tablet is indicated for adults and children aged 16 years and over.

4.2 Posology and method of administration

Posology

The daily dose should be taken all at once.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Exacerbations of osteoarthrosis: 7.5 mg/day. If necessary, in the absence of improvement, the dose may be increased to 15 mg/day.

Rheumatoid arthritis, ankylosing spondylitis: 15 mg/day. According to the therapeutic
response, the dose may be reduced to 7.5 mg/day (see also section ‘Special populations’
below).

DO NOT EXCEED THE DOSE OF 15MG/DAY.

Special populations

Elderly patients (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 (see also section 4.2 “Patients at increased risk of adverse effects” and section 4.4).

Patients with increased risks for adverse reaction (see section 4.4):
Patients with increased risks for adverse reactions, for example with a history of gastrointestinal pathologies or risk factors for cardiovascular pathologies, should start treatment with 7.5 mg per day.

Renal impairment (see section 5.2): This medicinal product is contraindicated in patients with severe renal impairment not on dialysis (see section 4.3). In patients with end-stage renal disease undergoing hemodialysis, the dosage should not exceed 7.5 mg/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).

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

Paediatric Population:
Meloxicam Tablets are contraindicated in children aged under 16 years (see section 4.3).

This medicine comes in other forms and strengths that may be more appropriate.

Method of administration
For oral use.

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

4.3 Contraindications

This medicinal product is contraindicated in the following situations:

- Third trimester of pregnancy (See section 4.6);
- Children and adolescents aged under 16;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- ***Hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Meloxicam 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 other 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);
- Severely impaired liver function;
- Non-dialysed severe renal failure;
- Gastrointestinal bleeding, history of cerebrovascular bleeding or other bleeding disorders;
- Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular risks below).

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven.

The use of meloxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Meloxicam is not appropriate for the treatment of patients requiring relief from acute pain.

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

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

Gastrointestinal effects

GI bleeding or ulceration/perforation, which can be fatal, have been reported related to the use of meloxicam as to other NSAIDs at any time during the treatment, with or without warning symptoms or a history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increased 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 section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI 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 heparin as curative treatment or given in geriatrics, oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or other non steroidal anti-inflammatory drugs including aspirin given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3g as total daily amount) (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Meloxicam tablets, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease
(ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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 oedema have been reported in association with NSAID therapy.

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

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

meloxicam.

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

Skin reactions

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of meloxicam.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, meloxicam treatment should be discontinued.
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of meloxicam, meloxicam must not be re-started in this patient at any time.

Liver and renal functional parameters

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin and other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory disturbances have 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.

Functional renal failure

NSAIDs cause a dose dependent inhibition of 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 may result in the decompensation of latent renal failure.

However, renal function returns to its initial status when treatment is withdrawn. This

particularly concerns patients with the following risk factors where monitoring of diuresis and renal function during treatment is necessary; (see sections 4.2

and 4.3).

- Elderly patient
- Congestive cardiac failure
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10)
- Nephrotic syndrome
- Renal failure
- Concomitant medications such as ACE inhibitors (e.g. ramipril, captopril), angiotensin-II antagonists - sartans (e.g. losartan, irbesartan, valsartan) and diuretics (e.g. bendroflumethiazide, furosemide) See section 4.5)
- Hypovolemia (whatever the cause)
- Lupus nephropathy

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

The dose of meloxicam 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).

Sodium, potassium and water retention
Induction of sodium, potassium and water retention and interference with the natriuretic
effects of diuretics and consequently possible exacerbations of the condition of patients with cardiac failure or hypertension may occur with NSAIDs. Furthermore, a decrease of the antihypertensive effect of antihypertensive drugs can occur (see section 4.5). Consequently, oedema, cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. Clinical monitoring is therefore necessary for patients at risk (see sections 4.2 and 4.3).

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

Combination with pemetrexed
In patients with mild to moderate renal insufficiency receiving pemetrexed, meloxicam should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

Other warnings and precautions

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

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

Meloxicam, as any other 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. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered (see section 4.6).

Lactose

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. that it is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Risks related to hyperkalemia

Certain medicinal products or therapeutic groups may promote hyperkalemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs, (low-molecular-weight or unfractionated) heparins, ciclosporin, tacrolimus and trimethoprim.

The onset of hyperkalemia may depend on whether there are associated factors. This risk is increased when the above-mentioned medicinal products are co-administered with meloxicam.

Pharmacodynamic Interactions:

Other NSAIDs (including cyclooxygenase-2 selective inhibitors) and Aspirin > 3g/d:
The combination (see section 4.4) with other non steroidal anti-inflammatory drugs, including aspirin given at anti-inflammatory doses (≥500 mg per dose or ≥ 3g as total daily amount) is not recommended, as administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding as a result of a synergistic effect.

Corticosteroids (e.g. Glucocorticoids):
Concomitant use with NSAIDs increases the risk of gastro-intestinal side-effects, such as bleeding or gastrointestinal ulceration.

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

In remaining cases of heparin use, caution is necessary due to an increased bleeding risk.

Careful monitoring of the INR is required if it proves impossible to avoid such combination.

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

Selective serotonin inhibitors:
Increased risk of gastrointestinal bleeding (see section 4.4)

Diuretics, ACE inhibitors and Angiotensin II Antagonists:
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function before initiation of concomitant therapy, and periodically thereafter (see also section 4.4).

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

Calcineurin inhibitors (e.g. ciclosporin, tacrolimus):
Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

Deferasirox
Concomitant administration of meloxicam and deferasirox may increase the risk of gastrointestinal adverse reactions. Caution is advised when combining these drugs.

Mifepristone:
NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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.

Quinolone antibiotics:
Animal data indicate that NSAIDs can increase the risk of convulsions associated with
quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Zidovudine:
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

<u>Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs)</u>

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 (15mg/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).

Pemetrexed
When using meloxicam concomitantly with pemetrexed in patients with creatinine clearance ranging from 45 to 79 ml/min, meloxicam treatment should be discontinued for at least five days before, on the same day, and at least two days after administration of pemetrexed. If co-administration of meloxicam and pemetrexed is necessary, patients should be carefully monitored, in particular because of the risk of myelosuppression and gastrointestinal adverse reactions. In patients with severe renal impairment (creatinine clearance less than 45 ml/min), the concomitant administration of meloxicam and pemetrexed is not recommended.

In patients with normal renal function (creatinine clearance ≥ 80 ml/min), doses of 15 mg meloxicam may decrease the elimination of pemetrexed and therefore increase the occurrence of adverse events due to pemetrexed. Therefore, caution should be taken when co-administering 15 mg doses of meloxicam with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 ml/min).

<u>Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)</u>

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.

Pharmacokinetic interactions: effects of the combination of meloxicam with other medicinal products on the pharmacokinetics

Oral antidiabetics (sulfonylureas, nateglinide)

Meloxicam is eliminated almost exclusively by hepatic metabolism, for which approximately two thirds is mediated by cytochrome (CYP) P450 enzymes (mainly CYP 2C9 and minor CYP3A4) and one third by other mechanisms such as oxidation. By peroxidase. The risk of occurrence of pharmacokinetic interaction must be taken into account when meloxicam is administered concomitantly with medicinal products known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4. Interactions via CYP 2C9 can be expected when combined with medicinal products such as oral antidiabetics (sulfonylureas, nateglinide), which may lead to increased plasma concentrations of these medicinal products and of meloxicam. Patients using meloxicam concomitantly with sulfonylureas or nateglinide should be carefully monitored for the risk of hypoglycaemia.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

prostaglandin synthesis inhibitor during the organogenetic period.

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

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

* the 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.

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

Fertility

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. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

There are no specific studies on the effects of meloxicam on the ability to drive and use machines. 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. If during the treatment, however, visual disturbances, dizziness,

fatigue, drowsiness or any CNS disturbance occur, it is recommended to avoid driving and using machines.

4.8 Undesirable effects

a) General Description

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

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

The most commonly-observed adverse events are gastrointestinal in nature. Gastroduodenal ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, anorexia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis, glossitis, pancreatitis, oesophagitis and oesophageal lesions have been observed.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

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.

b) Table of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention:
Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1.000); very rare (<1/10,000), not known (cannot be estimated from the available data) Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (see section c).

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

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

Nervous system disorders
Common: Headache
Uncommon: Dizziness, somnolence

Eye disorders
Rare: Visual disturbance including vision blurred; conjunctivitis

Ear and labyrinth disorders
Uncommon: Vertigo
Rare: Tinnitus

Cardiac disorders
Rare: Palpitations

Cardiac failure has been reported in association with NSAID treatment.

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

Respiratory, thoracic and mediastinal disorders
Rare: Asthma in 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
Not known: Pancreatitis

Gastrointestinal haemorrhage, ulceration or perforation may sometimes be severe and potentially fatal, especially in elderly (see section 4.4).

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

Skin and subcutaneous tissue disorders
Uncommon: Angioedema, pruritus, rash
Rare: Urticaria, Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) have been reported (see section 4.4)
Very rare: Dermatitis bullous, erythema multiforme
Not known: Photosensitivity reaction

Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalaemia (see section 4.4and section 4.5), renal function test abnormal (increased serum creatinine and/or serum urea)
Very rare: Acute renal failure in particular in patients with risk factors (see section 4.4.)

Reproductive system and breast disorders
Not known: female infertility, delayed ovulation

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

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

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

d) Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class:

Organic renal injury probably resulting in acute renal failure: very rare cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome, and papillary necrosis have been reported (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

a) Symptoms
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.

b) Therapeutic measures

In the event of NSAID overdose, appropriate symptomatic treatment should be instituted. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non Steroidal Anti-Inflammatory agent; Oxicams.
ATC Code: M01A C06.

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

Mechanism of Action
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

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 90% 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 (Cmin and Cmax 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 (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma.
Volume of distribution is low, on average 11 L after I/M or I.V administration and showsinter-individual variation is the order of 7 to 20%. The volume of distribution after administration of multiple oral doses of meloxicam (7.5 to 15 mg) is approximately 16 liters with coefficients of variation ranging from 11 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 CYP3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two

metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination

Meloxicam is excreted predominantly in the form of metabolites 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 variesbetween 13 and 25 hours after oral, I.M. and I. V. administration. Total plasma clearance is 7 to 12 ml/min after single doses, orally, intravenously or rectally .

Linearity/non-linearity

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

Special populations

Hepatic/renal insufficiency:

Neither hepatic nor mild or moderate renal insufficiency have a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significantly higher total drug clearance. Protein binding is reduced in patients with end stage renal disease. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded (see section 4.2).

Elderly:

Elderly males exhibited mean pharmacokinetic parameters similar to those of young males. Elderly females showed higher AUC values and longer elimination half-life compared to younger subjects of both sexes. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects (see section 4.2).

5.3 Preclinical safety data

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

Oral reproductive studies in the rat have shown inhibition of implantations and increase of resorptions of the foetus at high maternotoxic dose levels (1 mg/kg and higher). Reproductive toxicity studies in rats and rabbits did not show

teratogenic effects up to oral doses of 4mg/kg in rats and 80mg/kg in rabbits. The dose levels were 5-10-fold greater compared to the clinical dose (7.5-15 mg) in a 75 kg person. Foetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. Non-clinical studies have shown that meloxicam can be found in the milk of lactating animals. No evidence has been found of any mutagenic effect, either in vitro or in vivo. No carcinogenic effects have been found in the rat and mouse at doses far higher than those used clinically.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize starch
Pregelatinised starch
Colloidal anhydrous silica
Sodium citrate
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 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

10, 30 and 100 tablets in blister packs (PVC/PVDC/Aluminium).

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Flamingo Pharma UK Ltd.
1st floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA12AX, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/02/2006

10 DATE OF REVISION OF THE TEXT

30/03/2023