

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Melcam 15 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of meloxicam.

### Excipient with known effect

Each tablet contains 81.7 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

Pale yellow coloured round, flat bevelled uncoated tablets with central break-line on one side and plain on the other side.

The tablet can be divided into equal doses.

## 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.

Melcam is indicated in adults and children aged 16 years and older.

### 4.2 Posology and method of administration

#### Posology

The total daily amount should be taken as a single dose.

Undesirable effects may be minimised 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 osteoarthritis: 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 (see also section "Special populations" below).

According to the therapeutic response, the dose may be reduced to 7.5 mg/day.

DO NOT EXCEED THE DOSE OF 15 MG/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 "Patients with increased risks for adverse reactions" below and section 4.4).

##### *Patients with increased risks for adverse reaction (see section 4.4)*

In patients with increased risks for adverse reactions, e.g. a history of gastro-intestinal disease or risk factors for cardiovascular disease, the treatment should be started at a dose of 7.5 mg per day.

*Renal impairment (see section 5.2)*

This medicine is contraindicated in non-dialysed severe renal failure (see section 4.3).

In patients with end-stage renal failure on haemodialysis, 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).

*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*

Melcam is contraindicated in children and adolescents below 16 years of age (see section 4.3).

Method of administration

Oral use.

The tablets are swallowed with water or other fluid, during a meal.

**4.3 Contraindications**

This medicinal product is contra-indicated in the following situations:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- third trimester of pregnancy (see section 4.6)
- children and adolescents below 16 years of age
- hypersensitivity to substances with a similar action, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid. Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angioedema or urticaria following the administration of acetylsalicylic acid 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 minimised 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.

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 of the treatment 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

Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI 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 acetylsalicylic acid, or other medicinal products 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.

In patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as curative treatment or given in geriatrics, anticoagulants such as warfarin or other non-steroidal anti-inflammatory drugs or acetylsalicylic acid given at doses ( $\geq 500$  mg as single intake or  $\geq 3$  g as total daily amount the combination with meloxicam is not recommended (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving meloxicam 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 including meloxicam (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 including 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 medicinal product. 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.

#### Parameters of liver and renal function

As with most NSAIDs, occasional 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 and 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, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependant. At the beginning of the treatment, or after dose increase, careful monitoring of the renal function including the volume of diuresis is recommended in patients with the following risk factors:

- elderly

- concomitant treatments such as ACE inhibitors, angiotensin-II antagonists, sartans, diuretics (see section 4.5)
- hypovolaemia (whatever the cause)
- congestive heart failure
- renal failure
- nephrotic syndrome
- lupus nephropathy
- severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score  $\geq 10$ )

In rare instance 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 exceed 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 may occur with NSAIDs. Furthermore, a decrease of the antihypertensive effect of antihypertensive medicinal products 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 kalaemia (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, 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 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 may impair female 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).

#### Melcam contains lactose and sodium

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interactions**

#### Risks related to hyperkalaemia

Certain medicinal products or therapeutic groups may promote hyperkalaemia: 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 hyperkalaemia 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 non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid*

Combination (see section 4.4) with other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses ( $\geq 500$  mg as single intake or  $\geq 3$  g as total daily amount) is not recommended.

*Corticosteroids (e.g. glucocorticoids)*

The concomitant use with corticosteroids requests caution because of an increased risk of bleeding or gastrointestinal ulceration.

*Anticoagulants including heparin*

Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anti-coagulants, including coumarins (vitamin K antagonists) such as warfarin (see section 4.4), novel oral anticoagulants (NOACs) and heparin. The concomitant use of NSAIDs and heparin administered in geriatrics or at curative dose, or other anti-coagulants is not recommended (see section 4.4). In remaining cases (e.g. preventive doses) 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 medicinal products*

Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.

*Selective serotonin reuptake inhibitors (SSRIs)*

Increased risk of gastrointestinal bleeding.

*Diuretics, ACE inhibitors and Angiotensin-II antagonists*

NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. 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 antagonists 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 after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).

*Other antihypertensive medicinal products (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.

*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*

The concomitant administration of meloxicam with deferasirox may increase the risk of gastro-intestinal adverse reactions. Caution should be exercised when combining these medicinal products.

Pharmacokinetic interactions: Effect of meloxicam on the pharmacokinetics of other medicinal products*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 NSAIDs (see above) (see section 4.8).

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 severe renal impairment (creatinine clearance below 45 ml/min) the concomitant administration of meloxicam with pemetrexed is not recommended. In patients with normal renal function (creatinine clearance  $\geq 80$  ml/min), doses of 15 mg meloxicam may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be exercised when administering 15 mg meloxicam concurrently with pemetrexed to patients with normal function (creatinine clearance  $\geq 80$  ml/min).

Pharmacokinetic interactions: Effect of other medicinal products on the pharmacokinetics of meloxicamCholestyramine

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  $13 \pm 3$  hrs. This interaction is of clinical significance.

Pharmacokinetic Interactions: Effect of combination of meloxicam and of other drugs on the pharmacokineticsOral antidiabetics (sulphonylureas, nateglinide)

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 sulphonylureas or nateglinide should be carefully monitored for hypoglycemia.

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

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.

Breast-feeding

While no specific experience exists for meloxicam in humans, NSAIDs (non-steroidal anti-inflammatory drugs) are known to pass into mother's milk. Meloxicam has been found in the milk of nursing animals.

A risk cannot be ruled out and administration is not recommended in women who are breast-feeding.

#### Fertility

The use of meloxicam, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, may impair female 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.

#### **4.7 Effects on ability to drive and use machines**

No specific studies with respect to the effects on the ability to drive and use machinery have been performed. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on the ability to drive and use machines. However, when visual disturbances, dizziness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

#### **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 a small 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. Peptic ulcers, perforation or GI 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) have been reported following administration. Less frequently, gastritis has been observed.

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) 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.

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

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

##### b) Table of adverse reactions

| <b>System Organ Class</b>            | <b>Very common</b> | <b>Common</b> | <b>Uncommon</b>   | <b>Rare</b>  | <b>Very rare</b>                | <b>Not known</b>                              |
|--------------------------------------|--------------------|---------------|---|--|---------------------------------|---|
| Blood and lymphatic system disorders |                    |               | Anaemia   | Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia | Agranulocytosis (see section c) |   |
| Immune system disorders              |                    |               | Allergic reactions other than anaphylactic or anaphylactoid reactions |  |                                 | Anaphylactic reaction, anaphylactoid reaction |
| Psychiatric                          |                    |               |   | Mood altered,  |                                 | Confusional                                   |

|  |  |          |   |   |   |  |
|--|--|----------|---|---|---|--|
| disorders  |  |          |   | nightmares  |   | state,<br>disorientation                       |
| Nervous system disorders                                 |  | Headache | Dizziness,<br>somnolence  |   |   |  |
| Eye disorders  |  |          |   | Visual disturbance<br>including vision<br>blurred,<br>conjunctivitis                    |   |  |
| Ear and<br>labyrinth<br>disorders                        |  |          | Vertigo   | Tinnitus  |   |  |
| Cardiac<br>disorders                                     |  |          |   | Palpitations  |   | Cardiac failure*                               |
| Vascular<br>disorders                                    |  |          | Blood pressure<br>increased (see<br>section 4.4),<br>flushing   |   |   |  |
| Respiratory,<br>thoracic and<br>mediastinal<br>disorders |  |          |   | Asthma in<br>individuals allergic<br>to acetylsalicylic<br>acid or other<br>NSAIDs      |   |  |
| Gastrointestinal<br>disorders                            | Gastro<br>intestinal<br>disorders such<br>as dyspepsia,<br>nausea,<br>vomiting,<br>abdominal<br>pain,<br>constipation,<br>flatulence,<br>diarrhoea |          | Occult or<br>macroscopic<br>gastrointesti<br>nal<br>haemorrhage**,<br>stomatitis,<br>gastritis,<br>eructation   | Colitis,<br>gastroduodenal<br>ulcer**,<br>oesophagitis                                  | Gastro<br>intestinal<br>perforation**   | Pancreatitis                                   |
| Hepatobiliary<br>disorders                               |  |          | Liver function<br>disorder (e.g.<br>raised<br>transaminases or<br>bilirubin)  |   | Hepatitis   |  |
| Skin and<br>subcutaneous<br>tissue disorders             |  |          | Angioedema,<br>pruritus,<br>rash  | Stevens-Johnson<br>syndrome (SJS),<br>toxic epidermal<br>necrolysis (TEN),<br>urticaria | Dermatitis<br>bullous,<br>erythema<br>multiforme  | Photo<br>sensitivity<br>reaction               |
| Renal and<br>urinary<br>disorders                        |  |          | Sodium and water<br>retention,<br>hyperkalaemia<br>(see section 4.4<br>and section 4.5),<br>renal function test<br>abnormal<br>(increased serum<br>creatinine and/or<br>serum urea) |   | Acute renal<br>failure in<br>particular in<br>patients with<br>risk factors (see<br>section 4.4.) |  |
| <u>Reproductive<br/>system and<br/>breast disorders</u>  |  |          |   |   |   | Infertility<br>female,<br>ovulation<br>delayed |
| General<br>disorders and                                 |  |          | Oedema including<br>oedema of the   |   |   |  |



|                                |  |  |             |  |  |  |
|--------------------------------|--|--|-------------|--|--|--|
| administration site conditions |  |  | lower limbs |  |  |  |
|--------------------------------|--|--|-------------|--|--|--|

\* Cardiac failure has been reported in association with NSAID treatment

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

#### 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 medicinal products (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 HPRA Pharmacovigilance; website: [www.hpra.ie](http://www.hpra.ie).

## 4.9 Overdose

#### 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.

#### Treatment

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.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids; oxicams

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

#### Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent.

Following single dose administration of meloxicam, median 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 mean plasma concentrations of the active substance 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 for the tablet, capsule and the oral suspension, respectively. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

#### 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, 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 multiple oral doses of meloxicam (7.5 to 15 mg) is about 16 L 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 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 intramuscular administration.

#### Special populations

##### *Hepatic/renal Insufficiency*

Neither hepatic, nor mild to moderate renal insufficiency has a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significant 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 (see sections 4.2 and 4.3).

##### *Elderly*

Elderly male subjects exhibited similar mean pharmacokinetic parameters compared to those of young male subjects. Elderly female patients showed higher AUC-values and longer elimination half-lives compared to those of young subjects of both genders. 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 identical to that of NSAIDs: gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

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. 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.

The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on a 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 animals. 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**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

30 months

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

PVC/PVDC aluminium blisters.

Packs of 10, 20, 30, 50, 60 or 100 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Rowex Ltd  
Newtown  
Bantry  
Co. Cork  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0711/060/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 19 November 2004

Date of last renewal: 31 October 2008

## **10 DATE OF REVISION OF THE TEXT**

September 2020