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

For 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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Short-term symptomatic treatment of exacerbations of osteoarthrosis.

Long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

4.2. Posology and method of administration

For oral use.

- *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.

Recommended maximal daily dose (15 mg) should not be exceeded.

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

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 (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).

- *Children:* "Name" should not be used in children aged under 15.

4.3. Contraindications

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

- pregnancy and lactation (See section 4.6 Pregnancy and lactation).
- hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic edema 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.
- cerebrovascular bleeding or other bleeding disorders.
- severe heart failure.

4.4 Special warnings and special precautions for use

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

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

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 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).

Gastrointestinal bleeding, ulceration and perforation:
GI 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 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 aspirin, or other drugs likely to increase gastrointestinal risk (see below and 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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors, or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Meloxicam PSI, 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).

Skin reactions:
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 4.8). Patients appear to be at highest risk for 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.

Cases of fixed drug eruption (FDE) have been reported with meloxicam.

Meloxicam should not be reintroduced in patients with history of meloxicam-related FDE. Potential cross reactivity might occur with other oxicams.

Meloxicam PSI 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, 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.

• 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 (see sections 4.2 Posology and method of administration and 4.3 Contraindications).

• 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 cardiac failure, cirrhosis, nephrotic syndrome or renal failure as well as patients on diuretics or having undergone major surgery leading to hypovolemia. Careful monitoring of diuresis and renal function during treatment is necessary in such patients (see sections 4.2 Posology and method of administration and 4.3 Contraindications).

• Adverse reactions are often less well tolerated in elderly or in weakened individuals, who therefore require careful monitoring during Meloxicam treatment. 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 Meloxicam treatment should be reassessed.

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

• 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.

• 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.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions:

Other NSAIDs, including salicylates:
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).

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):
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.

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.

Ciclosporin:
Nephrotoxicity of ciclosporin 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 (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)

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 CYP 2C9 inhibitors, inducers and substrates:
Metabolic interactions possible.

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.

4.6. Pregnancy and lactation

Pregnancy

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

- It is advisable to avoid the administration of meloxicam during the first two trimesters of pregnancy.

- During the final three months, all prostaglandin synthesis inhibitors may expose the fetus 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 contra-indicated during the final three months.

Lactation
NSAIDs pass into mothers milk. Administration is contraindicated, as a precautionary measure, 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. If during the treatment, however, visual disturbances, dizziness, fatigue or any CNS disturbance occur, it is recommended to avoid driving and using machines.

4.8 Undesirable effects

a) General Description

The following adverse events, 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 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. < 1/10); uncommon ($\geq$ 1/1.000, < 1/100); rare ($\geq$ 1/10.000, < 1/1.000); 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 and vasculardisorders
Oedema, hypertension, and cardiac failure, have been reported in association

with NSAID treatment.

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).

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 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

Not known : Pancreatitis

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

Skin and subcutaneous tissue disorders
Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).
Not known – fixed drug eruption (see section 4.4)

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)

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

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).

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Non Steroidal Anti-Inflammatory agent, 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 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 (99%). 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 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 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 - 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. 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:
Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

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 fetus at high maternotoxic dose levels (1 mg/kg and higher). The dose levels were 5-10-fold greater compared to the clinical dose (7.5-15 mg) in a 75 kg person. 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 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
- starch, pregelatinised
- silica colloidal, anhydrous
- sodium citrate
- lactose monohydrate
- cellulose, micro-crystalline
- 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

6.5. Nature and contents of container

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

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Strandhaven Ltd. trading as Somex Pharma
600 High Road
Seven Kings
IG3 8B5 Ilford
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8. MARKETING AUTHORISATION NUMBER

PL 15764/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2005

10 DATE OF REVISION OF THE TEXT

28/11/2023