Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

MELOXICAM 7.5MG TABLETS
MELOXICAM 15MG TABLETS

Procedure No: UK/H/1135/001-2/DC

UK Licence No: PL 20532/0107-8

AUROBINDO PHARMA LIMITED

LAY SUMMARY

The MHRA granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Meloxicam 7.5 and 15mg Tablets (PL 20532/0107-8) on 11th December 2008. These are prescription only medicines (POM) that are used for the short-term treatment of symptoms associated with osteoarthritis, when this condition flares up, and the long-term treatment of the symptoms associated with rheumatoid arthritis and ankylosing spondilitis (a type of arthritis that causes pain and stiffness around the spine).

The active ingredient, meloxicam, belongs to a group of medicines called NSAIDs (non-steroidal anti-inflammatory drugs). These are used to reduce inflammation and associated pain.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Meloxicam 7.5 and 15mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Meloxicam 7.5 and 15mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Meloxicam
Form	Tablets for oral administration
Strength	7.5mg and 15mg
MA Holder	Aurobindo Pharma Limited Ares, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD, UK
Reference Member State (RMS)	UK
CMS	Belgium, Czech Republic, Germany, Greece, Finland, France, Hungary, Italy, Lithuania, the Netherlands, Poland, Portugal, Slovenia and Spain
Procedure Number	UK/H/1135/001-2/DC
Timetable	Day 210 – 27th October 2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Meloxicam 7.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 7.5 mg meloxicam.

Excipient: Lactose
Each 7.5 mg tablet contains 22.3 mg lactose (as lactose monohydrate).

3 PHARMACEUTICAL FORM
Tablet

Light yellow, round, uncoated tablet with score line between 'F' and '1' debossed on one side and plain on the other side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Short-term symptomatic treatment of exacerbation of osteoarthritis.
- Long-term symptomatic treatment of rheumatoid arthritis or of ankylosing spondylitis.

4.2 Posology and method of administration
Oral use.
The total daily amount should be taken as a single dose, with water or another liquid, during a meal.

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 osteoarthrosis: 7.5 mg per day. If necessary, in the absence of improvement, the dose may be increased to 15 mg per day.
- Rheumatoid arthritis, ankylosing spondylitis: 15 mg once daily (see also "Special populations").

Depending on the therapeutic effect, the dose may be reduced to 7.5 mg once daily.

DO NOT EXCEED A DAILY DOSE OF 15 MG.
Special populations
Elderly patients and patients with an increased risk of undesirable effects (see section 5.2):
For elderly patients the recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis is 7.5 mg per day. Patients with an increased risk of undesirable effects should start the treatment with 7.5 mg per day(see section 4.4).

Renal impairment (see section 5.2):
For dialysis patients with severe renal failure the dose should not exceed 7.5 mg per day. For patients with mild to moderate renal impairment (i.e. patients with creatinine clearance greater than 25 ml/min) a dose reduction is not required. (For patients with severe renal failure who are not on dialysis see section 4.3).

Hepatic impairment (see section 5.2):
A dose reduction is not required for patients with mild to moderate hepatic impairment. (For patients with severely impaired hepatic function, see section 4.3).

Children and adolescents (<15 years):
Meloxicam should not be used in children and adolescents under 15 years of age.

4.3 Contraindications

Meloxicam is contraindicated in the following situations:

- Hypersensitivity to meloxicam or to any of the excipients.
- Third trimester of pregnancy and lactation (see section 4.6).
- Hypersensitivity to substances with a similar effect, e.g. NSAIDs (Non steroidal anti inflammatory drugs), acetylsalicylic acid. Meloxicam should not be given to patients who, after taking acetylsalicylic acid or other NSAIDs, have had symptoms of asthma, nasal polyps, angioneurotic oedema or urticaria.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (i.e. two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure.
- Non-dialysed severe renal failure.
- Gastrointestinal haemorrhage, cerebrovascular haemorrhage or other bleeding disorders.
- Severe heart failure.

4.4 Special warnings and precautions for use

Meloxicam Aurobindo has a delayed delivery of meloxicam (5 - 6 hrs). This should be taken into account when a quick onset of efficacy (relief of pain) is demanded.

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

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

- Any history of esophagitis, 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, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or with out 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 medicinal product 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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (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).

- Alcohol may increase the risk of gastrointestinal bleeding and ulceration when used concomitantly with NSAIDs such as Meloxicam Aurobindo.

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).

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 NSAIDSs (see section 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. Meloxicam Aurobindo should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- 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 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, 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 diuresis and renal function 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)
- Hypovolemia (whatever the cause)
- Congestive heart failure
- Renal failure
- Nephrotic syndrome
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10)'

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

Sodium and water retention
Sodium and water retention with possibility of oedema, hypertension or hypertension aggravation, cardiac failure aggravation. Clinical monitoring is necessary, as soon as starting therapy in case of hypertension or cardiac failure. A decrease of the antihypertensive effect can occur (see section 4.5).

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 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.

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.

Impaired female fertility
The use of meloxicam, as with any medicinal product 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.

Meloxicam Aurobindo contains lactose monohydrate. 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 (acetylsalicyclic acid ≥ 3 g/day):
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).

Oral Anticoagulants:
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 oral anticoagulants is not recommended (see section 4.4). Careful monitoring of the INR (International normalized ratio) is required if it proves impossible to avoid such combination.

Thrombolytics and anti-platelet 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 (see section 4.4)

Corticosteroids:
Increased risk of gastrointestinal ulceration or 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 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 anti-hypertensive drugs (e.g. beta-blockers):
As for the latter, a decrease of the anti-hypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilator effect) can occur.

Cyclosporin:
Nephrotoxicity of cyclosporin 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.

Intrauterine devices (e.g. intrauterine coil):
NSAIDs have been reported to be able to decrease the efficacy of intrauterine devices. A decrease in the efficacy of intrauterine devices by NSAIDs has been previously reported, but further confirmation is required.

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 hematological toxicity of methotrexate can be amplified by treatment with NSAID preparations (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.

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

4.6 Pregnancy and lactation

Pregnancy:
Inhibition of prostaglandin synthesis might adversely affect the pregnancy and/or the embryo/fetal 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 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-fetal 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 trimesters 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 trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimesterof pregnancy, all prostaglandin synthesis inhibitors might expose the fetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which might 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 might 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.

Lactation:
NSAIDs pass into breast milk. For safety reasons administration of Meloxicam Aurobindo is therefore to be avoided in women who are breast-feeding (see section 4.3).

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

On the basis of the pharmacodynamic profile and reported undesirable effects, meloxicam is likely to have no or negligible influence on these abilities. However, when visual disturbances or drowsiness, dizziness or other central nervous system disturbances occur, it is recommended that driving or operating machinery be avoided.

4.8 Undesirable effects
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).

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

Gastrointestinal:
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. Pancreatitis has been reported very rarely.

a) General description
The frequencies given below are based on corresponding occurrences of reported adverse events in clinical trials. The information is based on clinical trials involving 3750 patients who were treated with daily oraldoses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

Undesirable 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)

b) Table of undesirable effects
Cardiac disorders
Uncommon: Palpitations
Very rare: Cardiac failure, myocardial infarction

Blood and the lymphatic system disorders
Common: Anaemia
Uncommon: Disturbances of blood count: leucocytopenia; thrombocytopenia; agranulocytosis (see section 'c')

Nervous system disorders
Common: Light-headedness, headache
Uncommon: Vertigo, tinnitus, drowsiness
Rare: Confusion

Eye disorders
Rare: Visual disturbances including blurred vision

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

The peptic ulcers, perforation or gastrointestinal bleeding that may occur can be fatal, especially in elderly patients (see section 4.4). Melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported.

Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalaemia, (see section 4.4 and section 4.5)
Rare: Acute functional renal failure in patients with risk factors (see section 4.4)

Skin and subcutaneous tissue disorders
Common: Pruritus, rash.
Uncommon: Urticaria.
Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions.

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

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

Immune system disorders
Rare: Anaphylactic / anaphylactoid reactions

Hepato-biliary disorders
Rare: Hepatitis

Psychiatric disorders
Rare: Mood disorders, insomnia and nightmares

Investigations
Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin). Disturbance of laboratory tests investigating renal function (e.g. raised creatinine or urea)

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 medicinal product s (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: isolated cases of intersticial nephritis, acute tubular necrosis, nephrotic syndrome and papillary necrosis have been reported (see section 4.4).

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: 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 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 medicinal product 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 medicinal product 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'-hydroxymethyl-meloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination

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

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

Linearity/non-linearity

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

Special populations
Hepatic/renal Insufficiency:
Neither hepatic, mild nor 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 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 in the number 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 at oral doses of up to 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. 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 the mouse at doses far higher than those used clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose microcrystalline
Sodium citrate
Crospovidone
Povidone (K 25)
Anhydrous colloidal silica
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
White opaque PVC/PVdC-Aluminium blisters.

Pack sizes:
6, 10, 12, 14, 20, 28, 30, 50, 60 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20532/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/12/2008

10 DATE OF REVISION OF THE TEXT

11/12/2008

1 NAME OF THE MEDICINAL PRODUCT

Meloxicam 15 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg meloxicam.

Excipient: Lactose
Each 15 mg tablet contains 19.0 mg lactose (as lactose monohydrate).

3 PHARMACEUTICAL FORM

Tablet

Light yellow, round, uncoated tablet with score line between 'F' and '2' debossed on one side and plain on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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 osteoarthrosis: 7.5 mg per day. If necessary, in the absence of improvement, the dose may be increased to 15 mg per day.
- Rheumatoid arthritis, ankylosing spondylitis: 15 mg once daily (see also "Special populations").

Depending on the therapeutic effect, the dose may be reduced to 7.5 mg once daily.

DO NOT EXCEED A DAILY DOSE OF 15 MG.

Special populations
Elderly patients and patients with an increased risk of undesirable effects (see section 5.2):
For elderly patients the recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis is 7.5 mg per day. Patients with an increased risk of undesirable effects should start the treatment with 7.5 mg per day(see section 4.4).

Renal impairment (see section 5.2):
For dialysis patients with severe renal failure the dose should not exceed 7.5 mg per day. For patients with mild to moderate renal impairment (i.e. patients with creatinine clearance greater than 25 ml/min) a dose reduction is not required. (For patients with severe renal failure who are not on dialysis see section 4.3).

Hepatic impairment (see section 5.2):
A dose reduction is not required for patients with mild to moderate hepatic impairment. (For patients with severely impaired hepatic function, see section 4.3).

Children and adolescents (<15 years):
Meloxicam should not be used in children and adolescents under 15 years of age.

4.3 Contraindications

Meloxicam is contraindicated in the following situations:

- Hypersensitivity to meloxicam or to any of the excipients.
- Third trimester of pregnancy and lactation (see section 4.6).
- Hypersensitivity to substances with a similar effect, e.g. NSAIDs (Non steroidal anti inflammatory drugs), acetylsalicylic acid. Meloxicam should not be given to patients who, after taking acetylsalicylic acid or other NSAIDs, have had symptoms of asthma, nasal polyps, angioneurotic oedema or urticaria.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (i.e. two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure.
- Non-dialysed severe renal failure.
- Gastrointestinal haemorrhage, cerebrovascular haemorrhage or other bleeding disorders.
- Severe heart failure.

4.4 Special warnings and precautions for use

Meloxicam Aurobindo has a delayed delivery of meloxicam (5 - 6 hrs). This should be taken into account when a quick onset of efficacy (relief of pain) is demanded.

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

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

- Any history of esophagitis, 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, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or with out 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 medicinal product 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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (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).

- Alcohol may increase the risk of gastrointestinal bleeding and ulceration when used concomitantly with NSAIDs such as Meloxicam Aurobindo.

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).

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 NSAIDSs (see section 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. Meloxicam Aurobindo should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- 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 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, 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 diuresis and renal function 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)
- Hypovolemia (whatever the cause)
- Congestive heart failure
- Renal failure
- Nephrotic syndrome
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10)'

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

Sodium and water retention
Sodium and water retention with possibility of oedema, hypertension or hypertension aggravation, cardiac failure aggravation. Clinical monitoring is necessary, as soon as starting therapy in case of hypertension or cardiac failure. A decrease of the antihypertensive effect can occur (see section 4.5).

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 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.

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.

Impaired female fertility
The use of meloxicam, as with any medicinal product 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.

Meloxicam Aurobindo contains lactose monohydrate. 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 (acetylsalicyclic acid ≥ 3 g/day):
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).

Oral Anticoagulants:
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 oral anticoagulants is not recommended (see section 4.4). Careful monitoring of the INR (International normalized ratio) is required if it proves impossible to avoid such combination.

Thrombolytics and anti-platelet 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 (see section 4.4)

Corticosteroids:
Increased risk of gastrointestinal ulceration or 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 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 anti-hypertensive drugs (e.g. beta-blockers):
As for the latter, a decrease of the anti-hypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilator effect) can occur.

Cyclosporin:
Nephrotoxicity of cyclosporin 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.

Intrauterine devices (e.g. intrauterine coil):
NSAIDs have been reported to be able to decrease the efficacy of intrauterine devices. A decrease in the efficacy of intrauterine devices by NSAIDs has been previously reported, but further confirmation is required.

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 hematological toxicity of methotrexate can be amplified by treatment with NSAID preparations (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.

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

4.6 Pregnancy and lactation

Pregnancy:
Inhibition of prostaglandin synthesis might adversely affect the pregnancy and/or the embryo/fetal 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 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-fetal 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 trimesters 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 trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimesterof pregnancy, all prostaglandin synthesis inhibitors might expose the fetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which might 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 might 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.

Lactation:
NSAIDs pass into breast milk. For safety reasons administration of Meloxicam Aurobindo is therefore to be avoided in women who are breast-feeding (see section 4.3).

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

On the basis of the pharmacodynamic profile and reported undesirable effects, meloxicam is likely to have no or negligible influence on these abilities. However, when visual disturbances or drowsiness, dizziness or other central nervous system disturbances occur, it is recommended that driving or operating machinery be avoided.

4.8 Undesirable effects

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).

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

Gastrointestinal:
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. Pancreatitis has been reported very rarely.

a) General description

The frequencies given below are based on corresponding occurrences of reported adverse events in clinical trials. The information is based on clinical trials involving 3750 patients who were treated with daily oraldoses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

Undesirable 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)

b) Table of undesirable effects

Cardiac disorders
Uncommon: Palpitations
Very rare: Cardiac failure, myocardial infarction

Blood and the lymphatic system disorders
Common: Anaemia
Uncommon: Disturbances of blood count: leucocytopenia; thrombocytopenia; agranulocytosis (see section 'c')

Nervous system disorders
Common: Light-headedness, headache
Uncommon: Vertigo, tinnitus, drowsiness
Rare: Confusion

Eye disorders
Rare: Visual disturbances including blurred vision

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
Common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea
Uncommon: Gastrointestinal bleeding, peptic ulcers, oesophagitis, stomatitis
Rare: Gastrointestinal perforation, gastritis, colitis
The peptic ulcers, perforation or gastrointestinal bleeding that may occur can be fatal, especially in elderly patients (see section 4.4). Melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported.

Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalaemia, (see section 4.4 and section 4.5)
Rare: Acute functional renal failure in patients with risk factors (see section 4.4)

Skin and subcutaneous tissue disorders
Common: Pruritus, rash.
Uncommon: Urticaria.
Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions.

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

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

Immune system disorders
Rare: Anaphylactic / anaphylactoid reactions

Hepato-biliary disorders
Rare: Hepatitis

Psychiatric disorders
Rare: Mood disorders, insomnia and nightmares

Investigations
Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin). Disturbance of laboratory tests investigating renal function (e.g. raised creatinine or urea)

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 medicinal product s (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: isolated cases of intersticial nephritis, acute tubular necrosis, nephrotic syndrome and papillary necrosis have been reported (see section 4.4).

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: 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 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 medicinal product 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 medicinal product 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'-hydroxymethyl-meloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination

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

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

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

Special populations
Hepatic/renal Insufficiency:
Neither hepatic, mild nor 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 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 in the number 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 at oral doses of up to 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. 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 the mouse at doses far higher than those used clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose microcrystalline
Sodium citrate
Crospovidone
Povidone (K 25)
Anhydrous colloidal silica
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
White opaque PVC/PVdC-Aluminium blisters.

Pack sizes:
6, 10, 12, 14, 20, 28, 30, 40, 50, 60 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20532/0108

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/12/2008

10 DATE OF REVISION OF THE TEXT
11/12/2008

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Meloxicam 7.5 mg tablets
Meloxicam 15 mg tablets
{Meloxicam}

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT MELOXICAM IS AND WHAT IT IS USED FOR

Meloxicam is one of a group of medicines called NSAIDs (non-steroidal anti-inflammatory drugs). Meloxicam reduces inflammation and pain.

Meloxicam is used for
- short-term treatment of the symptoms associated with osteoarthritis when this condition flares up.
- long-term treatment of the symptoms associated with rheumatoid arthritis and ankylosing spondylitis (a type of arthritis that causes pain and stiffness around the spine).

2. BEFORE YOU TAKE MELOXICAM

DO NOT take Meloxicam in the following circumstances
- **allergic** (hypersensitive) to meloxicam or any of the other ingredients of Meloxicam (please see section 6);
- history of asthma, nasal polyps (nasal obstruction due to swellings in the lining in your nose), urticaria (sudden swelling of the face and neck or skin rashes/nettle rash) following taking aspirin or other NSAIDs;
- if you are more than 6 months of pregnant or if you are breast-feeding;
- history of gastro-intestinal bleeding or perforation related to previous NSAIDs therapy;
- active, or history of recurrent peptic ulcer or haemorrhage;
- active inflammatory bowel disease (such as Crohn's disease or Ulcerative colitis);
- severe liver disease;
- non dialysed severe kidney disease;
- any bleeding disorder or a history of cerebrovascular bleeding (bleeding in the brain);
- severe heart disease

Meloxicam is not to be taken by children below 15 years of age.

If you are unsure whether any of the above apply to you please contact your doctor.

Take special care with Meloxicam

Warnings

Medicines such as Meloxicam may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

Meloxicam has a delayed delivery of meloxicam (5 - 6 hrs). This should be taken into account when a quick onset of efficacy (relief of pain) is demanded.

Precautions for use:

As it will be necessary to adjust the treatment, it is important to ask for your doctor's advice, before you take Meloxicam in case of:
- kidney, liver or heart problems (hypertension and/or heart failure) as well as fluid retention (please see also section 3),
- history of digestive disease (e.g. stomach or duodenal ulcer in the past)
- concomitant treatment with other medicines that increased the risk of peptic ulcer or bleeding, e.g. oral steroids, some antidepressants (those of the SSRI type, i.e. Selective Serotonin Reuptake Inhibitors), agents that prevent blood clots such as aspirin or anticoagulants such as warfarin. In such cases, consult your doctor before taking Meloxicam (See section Taking other medicines),
- intolerance to some sugars.

Meloxicam, as any other non-steroidal anti-inflammatory drug, may mask symptoms (e.g. fever) of an underlying infectious disease. Therefore, if you observe signs of an infection or should the symptoms worsen consult your doctor.

If you are a woman, Meloxicam may impair your fertility. Therefore you should not take if you are planning to become pregnant or if you have fertility problems / dosing fertility tests.

In elderly, the risk of side effects is higher, in particular for gastrointestinal bleeding, ulcers and perforations. Heart, liver and kidney functions should be closely monitored. The doses should be reduced.

Consult your doctor if any of the above warnings is applicable to you or has been in the past.

Taking other medicines

Please tell your doctor or pharmacist if you are currently taking or have recently taken any other medicines, including medicines obtained without a prescription, since there are some medicines that should not be taken together and others that may need their doses to be altered when taken together.

Always inform your doctor or pharmacist if you are using or receiving any of the following medicines before taking Meloxicam:
- acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs,
- corticosteroids,
- oral anticoagulants like warfarin, injectable heparin, antiplatelets drugs or other thrombolytics,
- lithium (used in mental illness)
- methotrexate (used to treat rheumatoid arthritis or cancer)
- medicines to treat high blood pressure (ACE inhibitors, diuretics, beta-blockers and angiotensin II antagonists),
- Selective Serotonin Reuptake Inhibitors
- cyclosporine (a medicine used to prevent transplant rejection after surgery),
- colestyramine (used to reduce cholesterol)

Co-administration of anti-inflammatory drugs, corticosteroids, medicines which prevent blood clotting (like warfarin or heparin, antiplatelet drugs) or which break down blood clots (thrombolytics) and certain anti-depressants (selective serotonin re-uptake inhibitors) may increase the risk of gastro-intestinal ulcers, bleeding and damage to the mucosa of the gut and stomach. Therefore the concomitant use of Meloxicam with these drugs is not recommended (see also sections "Take special care with Meloxicam" and section 4).

Tell your doctor if you are a woman using an intrauterine contraceptive device (IUD), usually known as a coil, as there may be a decrease of the efficacy of intrauterine devices with concomitant use of NSAIDs.

If you have any doubt about taking other medicines with Meloxicam, consult your doctor or pharmacist.

Taking Meloxicam with food and drink

Taking this medicine with alcohol may increase the risk of stomach ulcers and bleeding.

Ask your doctor or pharmacist for advice before taking alcohol with this medicine.

Pregnancy and breast-feeding

Do not take meloxicam if you are more than 6 months pregnant or if you are breast-feeding. Your doctor may prescribe meloxicam for you during early pregnancy as short-term use if they decide it is suitable.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

The tablets may make your vision blurred or make you feel drowsy or dizzy. If this happens you should not drive or use machines.

Important information about some of the ingredients of Meloxicam

Meloxicam contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE MELOXICAM

Always take Meloxicam exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Meloxicam are for oral use only. The total daily amount (according to the dosage tablet, please see below) should be swallowed as a single dose with water or another liquid during a meal.

Dosing:

The usual dose is
- short-term treatment of osteoarthritis: *7.5 mg (one tablet Meloxicam 7.5 mg / half tablet Meloxicam 15 mg) per day* . The dose may be increased – after consultation with your doctor- to 15 mg per day (two tablets Meloxicam 7.5 mg / one tablet Meloxicam 15 mg) per day. Depending on the therapeutic effect, the dose may be reduced to 7.5 mg.
- long term treatment of rheumatoid arthritis and ankylosing spondylitis: *15 mg (two tablets Meloxicam 7.5 mg / one tablet Meloxicam 15 mg)per day*. Depending on the therapeutic effect, the dose may be reduced to 7.5 mg.

Do not exceed the dose of 15 mg/day.

Please contact your doctor or pharmacist if you are not sure how to take this medicine or if you feel that the effect of Meloxicam is too strong or too weak.

Please note that this product is available in other strengths and pharmaceutical forms which may be more suitable for your treatment (please see section 6).

Information for elderly patients and for patients with restricted kidney and liver function

For elderly patients the recommended dose for long-term treatment of rheumatoid arthritis or ankylosing spondylitis is 7.5 mg per day. Also, patients at high risk of side effects should start treatment with 7.5 mg meloxicam/day.

If you have a severe kidney dysfunction and receive dialysis the maximum dose of Meloxicam should be 7.5 mg per day.

Meloxicam Tablets are not recommended for children *and adolescents* under 15 years of age.

If you take more Meloxicam than you should

If you take too much Meloxicam, contact your doctor or pharmacist immediately.

If you forget to take Meloxicam

If you have missed a dose, continue in accordance with your doctor's prescription. Never take a double dose of Meloxicam to make up for a forgotten dose.

If you stop taking Meloxicam

This class of anti-inflamatory drugs is not known to have any negetive consequences (so called rebound effects) if stopped suddenly, you should always check with your doctor or pharmacist if you are not sure.

If you have any further questions on the use this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Meloxicam can cause side effects, although not everybody gets them.

Medicines such as Meloxicam may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

Tell your doctor immediately if you notice any gastro-intestinal side effects at the start of the treatment (e.g stomach pain, heartburn), if you have previously suffered from any such side effects due to long term use of NSAIDs, and especially if you are elderly.

Stop immediately your treatment as soon as you notice the appearance of a skin rash, or any lesion on the mucous surface (e.g. the surface along the inside of the mouth), or any sign of allergy.

The list below includes all known side effects during treatment with meloxicam, including those experienced under by people taking higher than the recommended doses or long-term treatment. They have been ranked under headings of frequency using the following convention:

Common:	less than 1 in 10, but more than 1 in 100 patients treated (1-10%)
Uncommon:	less than 1 in 100, but more than 1 in 1000 patients treated (0.1-1%)
Rare:	less than 1 in 1000, but more than 1 in 10,000 patients treated (0.01-0.1%)
Very rare:	less than 1 in 10000 patients treated

Common side effects are:

- anaemia (reduction of the concentration of the red blood pigment haemoglobin)
- light-headedness
- headache
- upper abdominal complaints
- nausea and vomiting
- stomach ache
- constipation
- flatulence
- diarrhoea
- itch, skin rash
- oedema (accumulation of fluid in the tissues), including oedema of the lower leg

Uncommon side effects are:

- reduction in the number of blood platelets and reduction in the number of white blood cells
- dizziness
- tinnitus (ringing in the ears)
- drowsiness
- palpitations
- increase in blood pressure
- flushes
- wheals (urticaria)
- accumulation or retention of sodium and water in the body
- higher concentration of potassium in the blood (hyperkalaemia)
- temporary impairment of liver function values (e.g. raised transaminase or bilirubin levels)
- impairment in kidney function values (e.g. increased concentration of blood urea or creatinine)
- gastrointestinal bleeding,
- peptic ulcers
- stomatitis
- eructation
- oesophagitis

Rare side effects are:

- severe and sudden allergic reactions
- mood swings
- insomnia
- nightmares
- confusion
- disorientation
- vision disturbances including blurred vision
- conjunctivitis (inflammation of the conjunctiva)
- gastro-intestinal perforation, gastritis, colitis
- onset of asthma attacks in patients allergic to aspirin or to other NSAIDs
- hepatitis (inflammation of the liver)
- severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis/Lyell's syndrome)
- swelling of the skin and/or mucosa (angioedema)
- bullous reactions such as erythema multiforme
- photosensitivity (skin reactions triggered by exposure to light)
- acute renal failure in patients with risk factors.

Very rare side effects are:

- severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis/Lyell's syndrome)
- swelling of the skin and/or mucosa (angioedema)
- bullous reactions such as erythema multiforme
- photosensitivity (skin reactions triggered by exposure to light)
- heart failure, heart attack

In isolated cases a complete loss of certain blood cells (agranulocytosis) has been reported. Furthermore, during treatment with other NSAIDs, but not observed with Meloxicam, isolated cases of inflammation of the kidneys (interstitial nephritis) and certain kidney diseases (acute tubular necrosis, nephrotic syndrome, papillary necrosis) have been reported as side effects.

If any of these side effects gets serious or if you notice any side effects, which are not listed in this leaflet, please contact your doctor or pharmacist.

5. HOW TO STORE MELOXICAM

Keep out of the reach and sight of children.

Do not use Meloxicam after the expiry date, which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.
Do not use Meloxicam if you notice any visible signs of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Meloxicam contains

- The active substance is meloxicam.
  Each tablet contains 7.5 mg meloxicam.
  Each tablet contains 15 mg meloxicam.
- The other ingredients are sodium citrate, lactose monohydrate, microcrystalline cellulose, povidone K 25, anhydrous colloidal silica, crospovidone and magnesium stearate.

What Meloxicam looks like and contents of the pack

Tablet

Meloxicam 7.5 mg tablets are light yellow, round, uncoated tablet with score line between 'F' and '1' debossed on one side and plain on the other side.

Meloxicam 15 mg tablets are light yellow, round, uncoated tablet with score line between 'F' and '2' debossed on one side and plain on the other side. The tablet can be divided into two equal halves.

Meloxicam 7.5 mg tablets are available in packs of 6, 10, 12, 14, 20, 28, 30, 50, 60 and 100 tablets.

Meloxicam 15 mg tablets are available in packs of 6, 10, 12, 14, 20, 28, 30, 40, 50, 60 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

Manufacturer

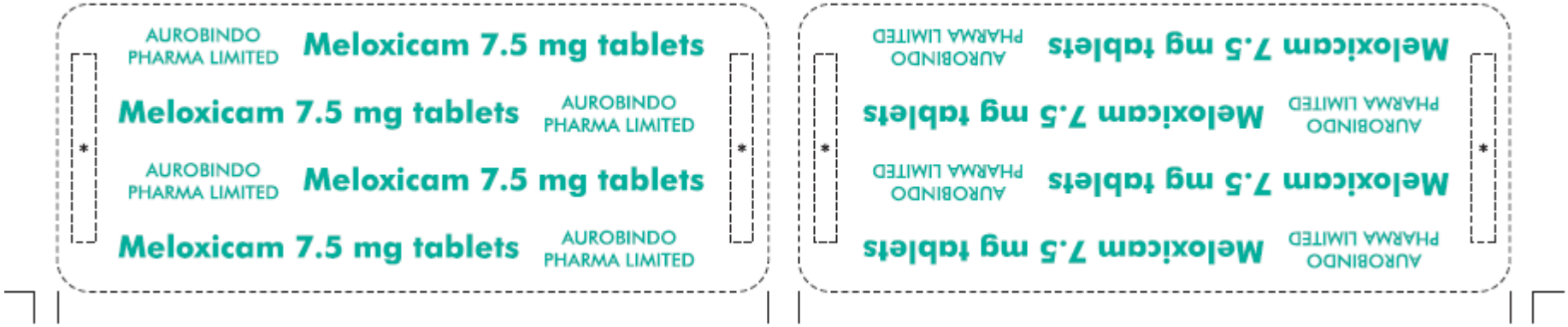
Milpharm Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

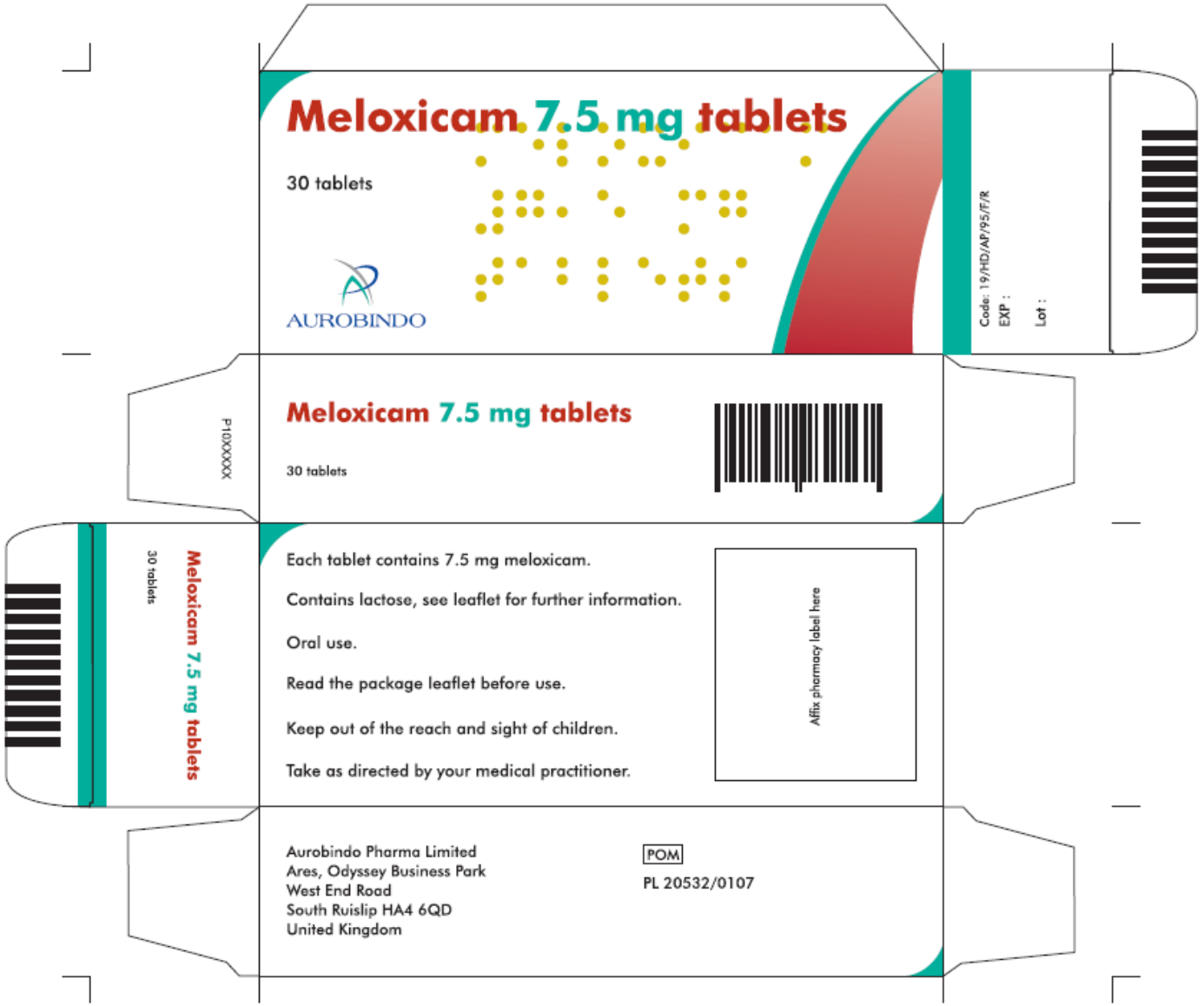
This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium:	Meloxicam Aurobindo 7,5 mg/15 mg tabletten
	Meloxicam Aurobindo 7,5 mg/15 mg comprimés
	Meloxicam Aurobindo 7,5 mg/15 mg Tabletten
Czech Republic:	Meloxicam Aurobindo 7,5 mg/15 mg tablety
Finland:	Meloxicam Aurobindo 7,5 mg/15 mg tabletti
	Meloxicam Aurobindo 7,5 mg/15 mg tabletter
France:	MELOXICAM AUROBINDO 7,5 mg/15 mg, comprimé
Germany:	Meloxicam Aurobindo 7,5 mg/15 mg Tabletten
Greece:	Meloxicam Aurobindo 7.5 mg/15 mg δισκία
Hungary:	Meloxicam Aurobindo 7,5 mg/15 mg tabletta
Italy:	Meloxicam Aurobindo 7,5 mg/15 mg Compresse
Lithuania:	Meloxicam Aurobindo 7,5 mg/15 mg tabletės
Poland:	Meloxicam Aurobindo 7,5 mg/15 mg
Portugal:	Meloxicam Aurobindo
Slovenia:	Meloksikam Aurobindo 7,5 mg/15 mg tablete
Spain:	Meloxicam Aurobindo 7,5 mg/15 mg comprimidos EFG
The Netherlands:	Meloxicam Aurobindo 7,5 mg/15 mg tabletten
United Kingdom:	Meloxicam 7.5 mg/15 mg tablets

This leaflet was last approved in 10/2008.

Module 4
Labelling




Meloxicam 7.5 mg tablets
30 tablets
AUROBINDO
Code: 19/HD/AP/95/F/R
EXP :
Lot :
XXXXXX-P1
Meloxicam 7.5 mg tablets
30 tablets
Meloxicam 7.5 mg tablets
30 tablets
Each tablet contains 7.5 mg meloxicam.
Contains lactose, see leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Take as directed by your medical practitioner.
Affix pharmacy label here
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom
POM
PL 20532/0107


AUROBINDO PHARMA LIMITED
Meloxicam 15 mg tablets
Meloxicam 15 mg tablets
AUROBINDO PHARMA LIMITED
AUROBINDO PHARMA LIMITED
Meloxicam 15 mg tablets
Meloxicam 15 mg tablets
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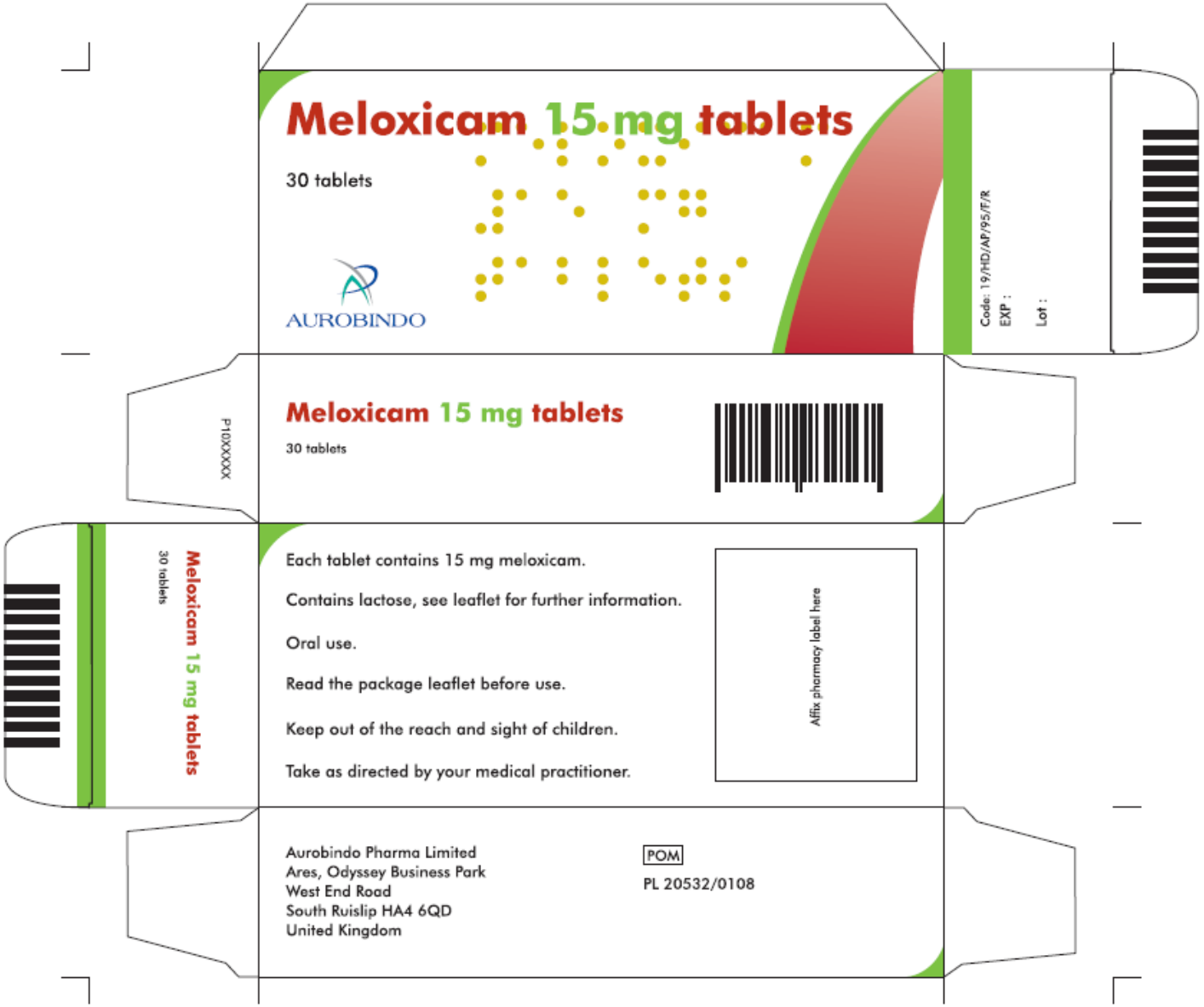
AUROBINDO PHARMA LIMITED


Meloxicam 15 mg tablets
30 tablets
AUROBINDO
Code: 19/HD/AP/95/F/R
EXP :
Lot :
P10XXXXX
Meloxicam 15 mg tablets
30 tablets
Meloxicam 15 mg tablets
30 tablets
Each tablet contains 15 mg meloxicam.
Contains lactose, see leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Take as directed by your medical practitioner.
Affix pharmacy label here
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom
POM
PL 20532/0108

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Meloxicam 7.5 and 15mg Tablets (PL 20532/0107-8; UK/H/1135/001-2/DC) could be approved. The products are prescription-only medicines for the short-term treatment of exacerbation of osteoarthritis and the long-term symptomatic treatment of rheumatoid arthritis or of ankylosing spondylitis.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products to Mobic 7.5 and 15mg Tablets (Boehringer Ingelheim, UK) which were granted UK licences over 10 years ago.

The active ingredient, meloxicam, is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam group, with anti-inflammatory, analgesic and antipyretic properties. Its precise mechanism of action remains unknown. However, the NSAIDs mechanism of action may be related to prostaglandin synthetase (cyclooxygenase, also known as COX inhibition), which leads to inhibition of biosynthesis of prostaglandins, known as inflammation mediators. Meloxicam is used for the treatment of osteoarthritis and rheumatoid arthritis.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Meloxicam 7.5mg Tablets Meloxicam 15mg Tablets
Name(s) of the active substance(s) (INN)	Meloxicam
Pharmacotherapeutic classification (ATC code)	Non-steroidal anti-inflammatory agent (M01A C06)
Pharmaceutical form and strength(s)	7.5 and 15mg tablets for oral administration
Reference numbers for the Mutual Recognition Procedure	UK/H/1135/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Czech Republic, Germany, Greece, Finland, France, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Slovenia and Spain
Marketing Authorisation Number(s)	PL 20532/0107-8
Name and address of the authorisation holder	Aurobindo Pharma Limited, Ares, Odyssey Business Park, West End Road, South Ruislip, HA4 6QD, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

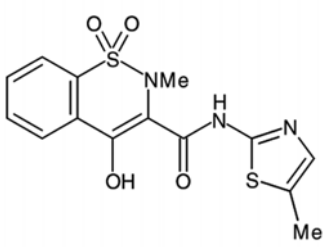
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Meloxicam

Chemical name: (i) 4-hydroxy-2-methyl-N-(5-methyl-1, 3-thiazol-2-y1)-2H- l, 2-benzothiazine-3- carboxamide l, 1 -dioxide.
(ii) 4-hydroxy-2-methyl-N-(5-methyl-2-thiazoly1)-2H- 1, 2-benzothiazine-3-carboxamide l-sulfone.

Structural formula:



Molecular formula: $C_{14}H_{13}N_3O_4S_2$

Appearance: A pale yellow powder, which is soluble in N, N-dimethylformamide, very slightly soluble in ethanol (96%) and is practically insoluble in water.

Molecular weight: 351.4

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance meloxicam. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance meloxicam.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, sodium citrate, crospovidone, povidone (K 25), colloidal anhydrous silica and magnesium stearate.

All excipients comply with their European Pharmacopoeia monograph. None of the excipients contain materials of animal or human origin, with the exception of lactose monohydrate. The supplier of lactose monohydrate has confirmed that the lactose used is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System
Both strengths of tablets are packaged in white opaque polyvinylchloride/polyvinylidene chloride/aluminium blisters contained in cardboard boxes. Pack sizes for both strengths are 6, 10, 12, 14, 20, 28, 30, 50, 60 and 100 tablets. The 40mg strength also has an additional pack size of 40 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food and the European Pharmacopoeia monograph concerning polyolefines.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no specific storage conditions.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place one commercial-scale batch per year on long-term stability.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

PHARMACODYNAMICS

Meloxicam, an acidic enolic non-steroidal anti-inflammatory drug (NSAID), has shown prominent anti-inflammatory action in animal models of rheumatoid arthritis. Preclinical evidence has shown a reduction in inflammatory paw swelling in the adjuvant arthritis rat model, inhibition of radiologically detectable bone and cartilage destruction, and inhibition of the systemic signs of immunologically induced inflammation (splenomegaly, changes in plasma protein composition, increase in erythrocyte sedimentation rate (ESR)).

In vitro, meloxicam was 3- to 300-fold more potent in inhibiting COX-2 than COX-1.

PHARMACOKINETICS

The pharmacokinetic data presented appear to be derived from human studies; this is acceptable as these data have superseded the animal data.

TOXICOLOGY

The toxicity of meloxicam is well-known and the main target organs are the gastrointestinal tract and the kidney, as expected for an NSAID. The non-clinical overview contains a discussion of the relationship to dose and duration of treatment of the induction of gastrointestinal lesions and ulceration, and the relevant plasma exposures.

There was no evidence to suggest that meloxicam has any tumorigenic effects when administered to rats or mice over a 2-year period.

Meloxicam was not mutagenic in a standard battery of *in vitro* and *in vivo* assays.

Reproductive studies in rats indicate that meloxicam has no effect on fertility and that embryotoxic effects (stillbirth and embryolethality) occur at doses that are also maternally toxic. As with other NSAIDs, the perinatal and postnatal periods appear to be critical because of the effects on parturition that result from inhibition of prostaglandin synthesis. These are known class effects for NSAIDs. In rabbits, meloxicam was embryolethal at high doses, but it was not teratogenic in one series of experiments. Another source revealed that oral doses 64.5 times the human dose at 15 mg/day for a 50-kg adult based on body surface area (human

dose) given throughout organogenesis resulted in an increased incidence of cardiac septal defects.

Constriction of the ductus ateriosus *in utero* is a pharmacologic consequence arising from the use of prostaglandin synthesis inhibitors during pregnancy.

Meloxicam is excreted into the milk of lactating rats at concentrations higher than those in the plasma. The molecular weight of meloxicam (about 351) is low enough that excretion into human milk should be expected.

No evidence of any immunogenic effects of meloxicam was seen in a guinea pig maximisation test on both the active substance and a gel formulation and in a local lymph node assay in mice.

Meloxicam was significantly less phototoxic than the NSAIDs, diclofenac, ketoprofen and naproxen, but similar to piroxicam and tenoxicam.

Extensive histological examinations on the hind legs of rats and mice exposed to maximum tolerated doses of meloxicam for the major part of their lives did not show any effect on the age-related osteoarthritic changes seen in these species. *In vitro* studies using pig cartilage and human cartilage preparations have demonstrated that meloxicam does not influence proteoglycan synthesis and metabolism suggesting that meloxicam does not have degenerative effects on cartilage.

EXCIPIENTS
The excipients are all are commonly used in tablet formulations and comply with the European Pharmacopoeia.

IMPURITIES/RESIDUAL SOLVENTS
Impurity levels in the active ingredient meloxicam are satisfactory. The active ingredient meloxicam is tested according to the British Pharmacopoeia. Any residual solvents used in the manufacturing process are controlled in accordance with current ICH guidelines.

ENVIRONMENTAL RISK ASSESSMENT
The applicant has conducted an Environmental Risk Assessment (ERA) calculation with satisfactory results. Since the product is a generic intended to replace the originator's product, it is not anticipated that it will increase the amount of active substance and its break-down products into the environment.

The ERA was conducted by an appropriately qualified person.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is satisfactory from a non-clinical viewpoint.

PRECLINICAL OVERVIEW
The Preclinical Overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ASSESSOR'S OVERALL CONCLUSION ON THE NON-CLINICAL PART

The Preclinical Overview has provided a satisfactory review of the data.

The toxicological properties of meloxicam are well-known. No adverse effects on cartilage were seen during the long-term studies in rats and mice, suggesting that meloxicam might be suitable for long-term use in osteoarthritis. Additionally, local tolerance studies showed that the meloxicam formulations tested exhibit good tissue tolerability.

The Preclinical Overview does not contain an assessment of whether the applicant's data support a claim of essential similarity. However, it is accepted that the product is a straightforward tablet formulation, there are no issues in respect of the excipients, impurities or residual solvents and there are no preclinical objections to the grant of a licence.

III.3 CLINICAL ASPECTS

Pharmacokinetics

To support the applications, the marketing authorisation holder has submitted two single-dose bioequivalence studies.

An open-label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of the test product Meloxicam 15mg tablets (Aurobindo Pharma Ltd) versus the reference product Mobic 15mg tablets (Boehringer Ingelheim Pharma Limited, UK) in healthy, adult, male, human subjects under fed conditions.

All subjects fasted overnight and were given a high-fat, high-calorie breakfast 30 minutes before dosing. Blood samples were taken pre- and up to 120 hours post dose, with a washout period of at least 9 days between doses.

Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values and geometric means:

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Meloxicam			
Test	34,927.09	37,278.31	1144.43
Reference	34,944.10	37,706.66	1038.32
Ratio (90% CI)	99.95 (95.13; 105.02)	98.86 (94.12; 103.85)	110.22 (105.39; 115.27)

The results for the primary variables indicate that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for active meloxicam lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

An open-label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of the test product Meloxicam 7.5mg tablets (Aurobindo Pharma Ltd) versus the reference product Mobic 7.5mg tablets (Boehringer Ingelheim Pharma Limited, UK) in healthy, adult, male, human subjects under fed conditions.
All subjects fasted overnight and were given a high-fat, high-calorie breakfast 30 minutes before dosing. Blood samples were taken pre- and up to 120 hours post dose, with a washout period of at least 9 days between doses.

Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values and geometric means:

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Meloxicam			
Test	26,953.90	29,323.15	1026.14
Reference	28,521.88	30,578.19	1022.62
Ratio (90% CI)	94.50 (91.02; 98.12)	95.90 (92.54; 99.37)	100.34 (94.59; 106.45)

The results for the primary variables indicate that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for active meloxicam lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

Efficacy
No new data on the efficacy of meloxicam are submitted and none are required for these types of application.

Safety
With the exception of the safety findings in the bioequivalence studies, no new data on the safety of meloxicam are submitted and none are required for these types of application. The safety findings in the bioequivalence studies were comparable between the test and reference products. The recorded safety profile of the active remains satisfactory when used for the proposed indications and at the recommended dosages.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

MAA Forms
The MAA forms are satisfactory from a medical viewpoint.

Clinical Expert Report
The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Meloxicam 7.5 and 15mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk/benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Meloxicam 7.5 and 15mg Tablets and the originator products Mobic 7.5 and 15mg Tablets (Boehringer Ingelheim Pharma Limited, UK).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Mobic Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with meloxicam is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome