Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

MELOXICAM 7.5MG TABLETS
MELOXICAM 15MG TABLETS

Procedure No: UK/H/1117/001-2/DC

UK Licence No: PL 30867/0001-2

TABUK POLAND SP.ZO.O.

LAY SUMMARY

The MHRA granted Tabuk Poland Sp. z.o.o Marketing Authorisations (licences) for the medicinal products Meloxicam 7.5 and 15mg Tablets (PL 30867/0001-2) on 13th February 2009. These are prescription only medicines (POM) that are used for the short-term treatment of symptoms associated with osteoarthritis (a joint disease where the cartilage is lost), when this condition flares up, and the long-term treatment of the symptoms associated with rheumatoid arthritis and ankylosing spondylitis (a type of arthritis that causes inflammation of the spine).

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

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	Tabuk Poland Sp. z.o.o, ul. Capri 2, lok. 77, 02-762 Warszawa, Poland
Reference Member State (RMS)	UK
CMS	Czech Republic, Hungary and Poland
Procedure Number	UK/H/1117/001-2/DC
Timetable	Day 210 – 8th December 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.

This product contains 40.85 mg lactose per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Pale yellow coloured round tablet with a score line on one side.

The score line 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.

Exacerbations of osteoarthrosis: 7.5 mg/day (one tablet of 7.5 mg).

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

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

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

DO NOT EXCEED THE DOSE OF 15 mg/day.

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

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

Renal impairment (see section 5.2):
In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day.

No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure who are not on dialysis see section 4.3).

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

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

This medicinal product exists in other strengths which may be more appropriate.

4.3 Contraindications

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

- third trimester of pregnancy and lactation (see section 4.6).
- hypersensitivity to meloxicam or any of its excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, acetylsalicylic acid (e.g. aspirin). Meloxicam tablets should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria, following administration of acetylsalicylic acid (e.g. aspirin) or other NSAIDs.
- active gastrointestinal ulcer or history of recurrent gastrointestinal ulcer;
- severely impaired liver function;
- non-dialysed severe renal failure;
- gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders;
- severe heart failure

4.4 Special warnings and precautions for use

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

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 drugs likely to increase gastrointestinal risk (see below and section 4.5).

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as 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 – undesirable effects).

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 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 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 Interaction with other medicinal products and other forms of interaction)
- 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.

The use of meloxicam, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions:

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

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding.

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

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 vasodilatory effect) can occur.

Cyclosporins:
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:
A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported, but needs further confirmation.

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

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

The risk of an interaction between NSAID preparations and methotrexate should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary, blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs (see above). (See section 4.8).

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam):
Cholestyramine:
Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.

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 may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, meloxicam should not be given unless clearly necessary. If meloxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Lactation:
While no specific experience exists for meloxicam, NSAIDs are known to pass into mother's milk. Administration is contraindicated in women who are breast-feeding.

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. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on these abilities. However, when visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

4.8 Undesirable effects

a) General Description

The frequencies of adverse drug reactions 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 have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

Adverse drug reactions that have come to light as a result of reports received in relation to administration of the marketed product are included.

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

1. Very common (≥ 1/10);
2. common (≥ 1/100, < 1/10);
3. uncommon (≥ 1/1000, < 1/100);
4. rare (≥ 1/10000, < 1/1000);
5. very rare (< 1/10000)

b) Table of adverse reactions

Blood and the lymphatic system disorders

Common: Anaemia

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

Immune system disorders

Rare: Anaphylactic/anaphylactoid reactions

Psychiatric disorders

Rare: Mood disorders, insomnia and nightmares

Nervous system disorders

Common: Light-headedness, headache

Uncommon: Vertigo, tinnitus, drowsiness

Rare: Confusion

Eye disorders

Rare: Visual disturbances including blurred vision

Cardiac disorders

Uncommon: Palpitations, cardiac failure

Vascular disorders

Uncommon: Hypertension (see section 4.4), flushes

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).

Respiratory, thoracic and mediastinal disorders

Rare: Onset of asthma attacks in certain individuals allergic to acetylsalicylic acid (e.g. aspirin) or other NSAIDs

Gastrointestinal disorders

Common: Dyspepsia, nausea and vomiting symptoms, abdominal pain, constipation, flatulence, diarrhoea

Uncommon: Gastrointestinal bleeding, gastrointestinal ulcers, oesophagitis, stomatitis

Rare: Gastrointestinal perforation, gastritis, colitis

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

Hepato-biliary disorders

Rare: Hepatitis

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

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)

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

Investigations
Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin)
Uncommon: 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 drugs (see section 4.5).

d) Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class
Organic renal injury probably resulting in acute renal failure: isolated cases of interstitial 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 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 drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake

Distribution
Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11%. Interindividual variation is the order of 30-40%.

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

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

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

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

Special populations
Hepatic/renal Insufficiency:
Neither 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 up to 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 mouse at doses far higher than those used clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Pregelatinised Maize Starch
Lactose Monohydrate
Maize Starch
Sodium Citrate Dihydrate
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister of PVC/PVdC and hard tempered Aluminium foil. Cartons of 7, 10, 14, 20, 30, 60, and 100 tablets, (not all pack sizes may be marketed).

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tabuk Poland Sp. z.o.o
ul. Capri 2,
lok. 77, 02-762 Warszawa
Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30867/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2009

10 DATE OF REVISION OF THE TEXT

13/02/2009

1 NAME OF THE MEDICINAL PRODUCT

Meloxicam 15 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 15 mg meloxicam.

This product contains 81.7 mg lactose per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pale yellow coloured round tablet with a score line on one side.

The tablet can be divided 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.

Exacerbations of osteoarthrosis: 7.5 mg/day (one tablet of 7.5 mg).

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

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

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

DO NOT EXCEED THE DOSE OF 15 mg/day.

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

Special populations

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

Renal impairment (see section 5.2):
In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day.

No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure who are not on dialysis see section 4.3).

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

Children and adolescents (<15 years):
Meloxicam should not be used in children aged under 15 years.
This medicinal product exists in other strengths which may be more appropriate.

4.3 Contraindications

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

- third trimester of pregnancy and lactation (see section 4.6).
- hypersensitivity to meloxicam or any of its excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, acetylsalicylic acid (e.g. aspirin). Meloxicam tablets should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria, following administration of acetylsalicylic acid (e.g. aspirin) or other NSAIDs.
- active gastrointestinal ulcer or history of recurrent gastrointestinal ulcer;
- severely impaired liver function;
- non-dialysed severe renal failure;
- gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders;
- severe heart failure

4.4 Special warnings and precautions for use

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

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 drugs likely to increase gastrointestinal risk (see below and section 4.5).

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as 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 – undesirable effects).

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 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 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 Interaction with other medicinal products and other forms of interaction)
- 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.

The use of meloxicam, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions:

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

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding.

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

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 vasodilatory effect) can occur.

Cyclosporins:
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:
A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported, but needs further confirmation.

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

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

The risk of an interaction between NSAID preparations and methotrexate should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary, blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs (see above). (See section 4.8).

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam):
Cholestyramine:
Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.

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 may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, meloxicam should not be given unless clearly necessary. If meloxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Lactation:
While no specific experience exists for meloxicam, NSAIDs are known to pass into mother's milk. Administration is contraindicated in women who are breast-feeding.

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. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, meloxicam is likely to have no or negligible influence on these abilities. However, when visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

4.8 Undesirable effects

a) General Description
The frequencies of adverse drug reactions 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 have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

Adverse drug reactions that have come to light as a result of reports received in relation to administration of the marketed product are included.

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

1. Very common (≥ 1/10);
2. common (≥ 1/100, < 1/10);
3. uncommon (≥ 1/1000, < 1/100);
4. rare (≥ 1/10000, < 1/1000);
5. very rare (< 1/10000)

b) Table of adverse reactions

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

Immune system disorders
Rare: Anaphylactic/anaphylactoid reactions

Psychiatric disorders
Rare: Mood disorders, insomnia and nightmares

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

Eye disorders
Rare: Visual disturbances including blurred vision

Cardiac disorders
Uncommon: Palpitations, cardiac failure

Vascular disorders
Uncommon: Hypertension (see section 4.4), flushes

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).

Respiratory, thoracic and mediastinal disorders
Rare: Onset of asthma attacks in certain individuals allergic to acetylsalicylic acid (e.g. aspirin) or other NSAIDs

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

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

Hepato-biliary disorders
Rare: Hepatitis

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

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)

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

Investigations
Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin)
Uncommon: 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 drugs (see section 4.5).

d) Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class
Organic renal injury probably resulting in acute renal failure: isolated cases of interstitial 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 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 drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake

Distribution
Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11%. Interindividual variation is the order of 30-40%.

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

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

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

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

Special populations
Hepatic/renal Insufficiency:
Neither 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 up to 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 mouse at doses far higher than those used clinically.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Pregelatinised Maize Starch
Lactose Monohydrate
Maize Starch
Sodium Citrate Dihydrate
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

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

6.5 Nature and contents of container
Blister of PVC/PVdC and hard tempered Aluminium foil. Cartons of 7, 10, 14, 20, 30, 60, and 100 tablets, (not all pack sizes may be marketed).

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Tabuk Poland Sp. z.o.o
ul. Capri 2,
lok. 77, 02-762 Warszawa
Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30867/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/02/2009

10 DATE OF REVISION OF THE TEXT
13/02/2009

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, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:

1. What Meloxicam tablets are and what they are used for

Meloxicam belongs to the group of non-steroidal anti-inflammatory drugs (NSAID) used for the treatment of pain and to reduce inflammatory conditions in muscles and joints.

Meloxicam tablets have been approved for:
• the short-term treatment of the symptoms of flare-ups of osteoarthrosis (joint disease where the cartilage is lost)
• the long-term treatment of the symptoms of rheumatoid arthritis
• the long-term treatment of the symptoms of a similar condition called ankylosing spondylitis (inflammation of the spine).

2. Before you take Meloxicam tablets

Do not take Meloxicam tablets:
- during the last trimes ter of pregnancy and while breast-feeding
- if you are allergic (hypersensitive) to meloxicam or any of the other ingredients of Meloxicam tablets
- if you are allergic to acetylsalicylic acid (e.g. aspirin) or other non-steroidal anti- inflammatory drugs (NSAID)
- if you have, or have had, recurrent ulcer of the stomach or duodenum (small intestine)
- if you have bleeding in the bowels, bleeding from vessels in the brain or other bleeding disorders
• if you have severe liver problems
• if you have severe kidney failure and you are not receiving dialysis
• if you suffer from severe heart failure.

Take special care with Meloxicam tablets and talk to your doctor:
• if you have a history of problems with your stomach or gut
• if you are elderly
• if you have recently undergone major surgery
• if you have liver, kidney or heart problems
• if you suffer from raised potassium levels in the blood
• if you have a history of asthma
• if you have an IUD (intra-uterine device e.g. coil) fitted for contraception
• if you notice blood in your faeces (stools)
• if you notice any skin reaction
• if you have to take a blood or urine test, always mention that you are taking meloxicam
• if you are trying to become pregnant or undergoing investigations of infertility as meloxicam can impair fertility
• if you have a history of stomach or gut ulcer or inflammation.

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, as with other non-steroidal anti-inflammatory drugs (NSAID) may mask the symptoms of an underlying infectious disease.

Taking other medicines:
Tell your doctor if you are taking any of the following:
anticoagulants, to stop your blood clotting, such as warfarin, heparin and ticlopidine
•other non-steroidal anti-inflammatory drugs (NSAID) such as aspirin
• lithium (for mental illness)
• methotrexate (for psoriasis and some cancers)
•thrombolytics (for heart conditions to dissolve blood clots)
•cholestyramine (for reducing cholesterol)
•ciclosporin (an immunosuppressant)
•diuretics (water tablets)
•medicines to treat high blood pressure.
•corticosteroids (for asthma, inflammation and after organ transplant surgery).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Meloxicam tablets with food and drink
Meloxicam tablets should be swallowed whole with water during a meal.

Pregnancy and breast-feeding:
Ask your doctor before taking meloxicam during the first two trimesters of pregnancy. Because of an increased risk of complications for mother and child, do not take meloxicam during the last trimester of pregnancy.
Do not take meloxicam while breast-feeding.

Driving and using machines:
Meloxicam tablets may cause side effects that may affect a person's ability to drive and use machinery. Examples of side effects include visual disturbances, drowsiness or dizziness. If you suffer from any of these side effects it is advisable to refrain from driving or using machinery.

Important information about some of the ingredients of Meloxicam tablets:
This drug 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 tablets

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

The recommended dose for the treatment of the symptoms of flare-ups of osteoarthrosis is 7.5 mg/day (one 7.5 mg tablet or half a 15 mg tablet). This may be increased by your doctor to 15 mg/day (two 7.5 mg tablets or one 15 mg tablet) if the effect is too weak.

The recommended dose for the treatment of the symptoms of rheumatoid arthritis and ankylosing spondylitis is 15 mg/day (two 7.5 mg tablets or one 15 mg tablet). This may be reduced to 7.5 mg/day (one 7.5 mg tablet or half a 15 mg tablet) depending on your response to treatment.

Never exceed a dose of 15 mg a day.

In dialysis patients with severe kidney failure, dosage should not exceed one tablet of 7.5 mg a day.

If you are elderly your doctor may recommend a lower dose. Children and adolescents under the age of 15 years should not take Meloxicam tablets.

Take Meloxicam tablets orally as a single dose with water and together with a meal.

Duration of treatment:
Your doctor will advise you of the duration of treatment.

If you take more Meloxicam tablets than you should:
Contact your doctor or local emergency ward. Take this leaflet and any tablets you still have with you. Symptoms of overdose include feeling tired and drowsy, nausea, vomiting, stomach pain, gastrointestinal bleeding, high blood pressure, kidney failure, liver problems, breathing difficulties, coma, convulsions, heart problems and severe allergic reactions.

If you forget to take Meloxicam tablets:
If you forget to take a dose, take it as soon as you remember it unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Meloxicam tablets:
Stopping your medicine before finishing the course of treatment may cause your pain or inflammation to get worse. It is important not to stop taking your medicine without prior discussion with your doctor.

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

4. Possible side effects

Like all medicines, Meloxicam tablets can cause side effects, although not everybody gets them. The following side effects have been reported:

Common side effects (seen in more than 1 in 100 patients but less than 1 in 10 patients) include: anaemia (looking pale and feeling abnormally tired), light-headedness, headache, indigestion, feeling sick, vomiting, stomach pain, constipation, wind, diarrhoea, intense itching, rash, and swelling especially of the lower limbs.

Uncommon side effects (seen in more than 1 in 1,000 patients but less than 1 in 100 patients) include: blood changes, vertigo, ringing in the ears, drowsiness, palpitations, cardiac failure, increased blood pressure, feeling flushed, blood in your faeces (stools), ulcers of the stomach and small intestine, inflammation of the oesophagus (food pipe) symptoms include heartburn and a difficulty swallowing, sore mouth or mouth ulcers, changes to kidney or liver function tests, itchy swollen skin, sodium and water retention and increased levels of potassium in the blood.

Rare side effects (see in more than 1 in 10,000 patients but less than 1 in 1,000) include: severe allergic reaction, mood disorders, difficulty sleeping, nightmares, feeling confused, eyesight problems such as blurred vision, asthma attacks, pain due to tearing of the stomach or gut wall, inflamed stomach or colon, hepatitis (liver problems), severe skin reactions (such as rash, fever and blistering), skin sensitivity to light and kidney failure. Seek immediate medical advice if symptoms of anaphylactic reactions (for example swelling of the face and lips or difficulty in breathing) or serious skin reactions occur.

Meloxicam may cause a reduction in the number of white blood cells and your resistance to infection may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

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

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.

5. How to store Meloxicam tablets

Keep out of the reach and sight of children.
Do not use Meloxicam tablets after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions.

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 tablets contain:
The active substance is meloxicam. Each 7.5 mg tablet contains meloxicam 7.5 mg. Each 15 mg tablet contains meloxicam 15 mg.
The other ingredients are microcrystalline cellulose, pregelatinised maize starch, lactose monohydrate, maize starch, sodium citrate dihydrate, colloidal anhydrous silica and magnesium stearate.

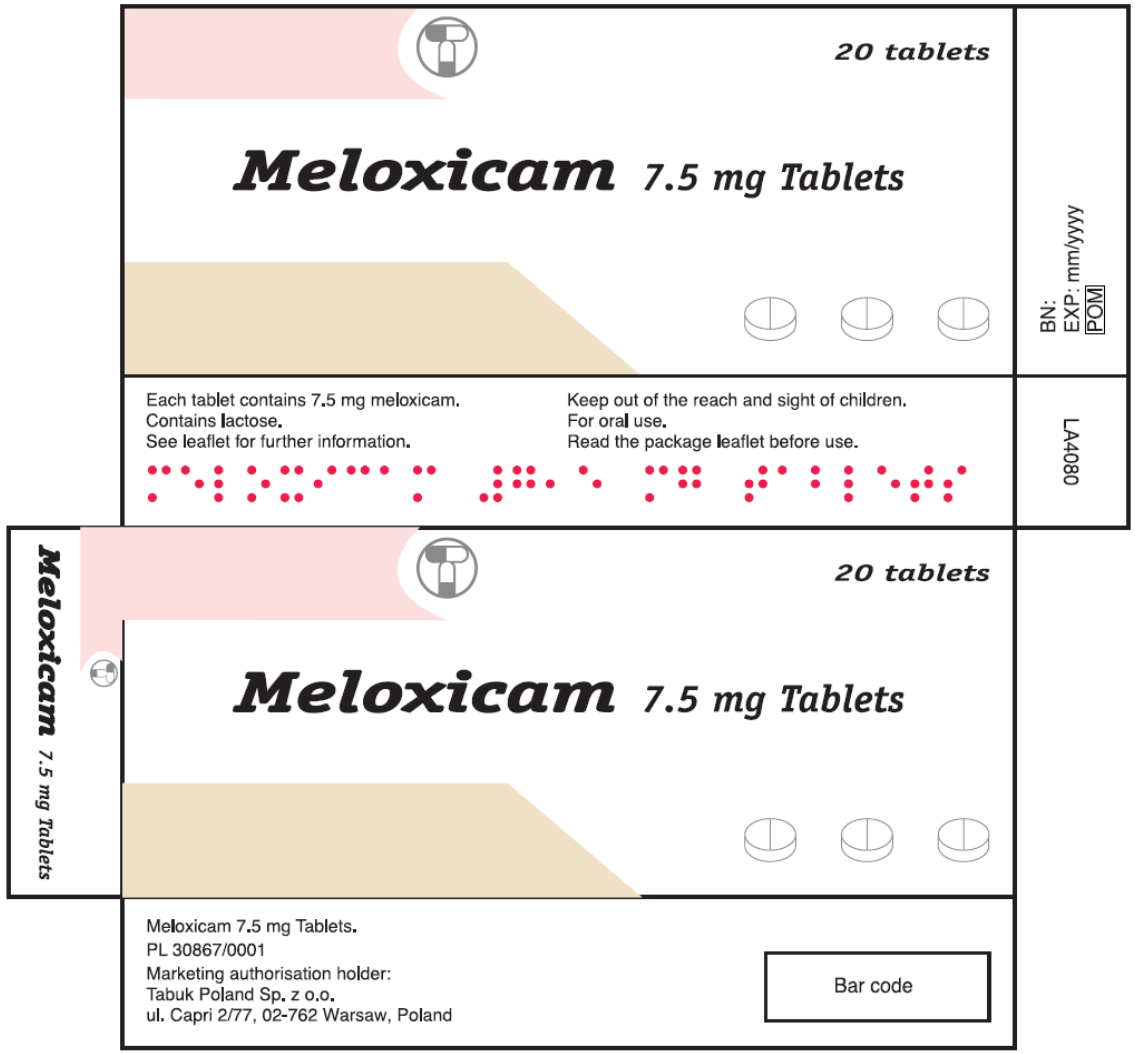
What Meloxicam tablets look like and contents of the pack:
Meloxicam tablets are pale yellow, round tablets with a score on one side. They come in packs of 7, 10, 14, 20, 30, 60, and 100 tablets (not all pack sizes may be marketed).

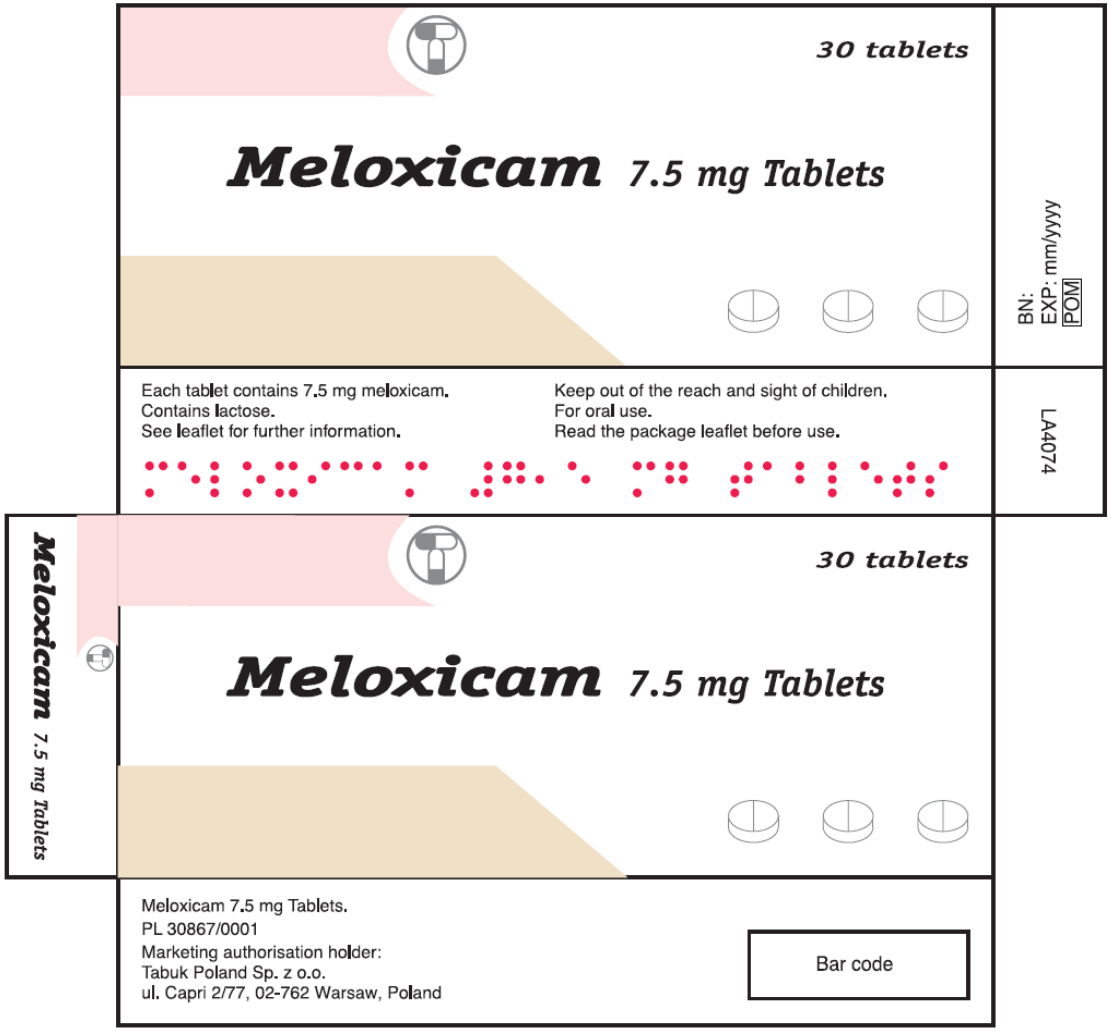
Marketing Authorisation Holder and Manufacturer:
The marketing authorisation holder is Tabuk Poland Sp. z.o.o., Warsaw, Poland.
The manufacturer is Chanelle Medical, Loughrea, Co. Galway, Ireland.

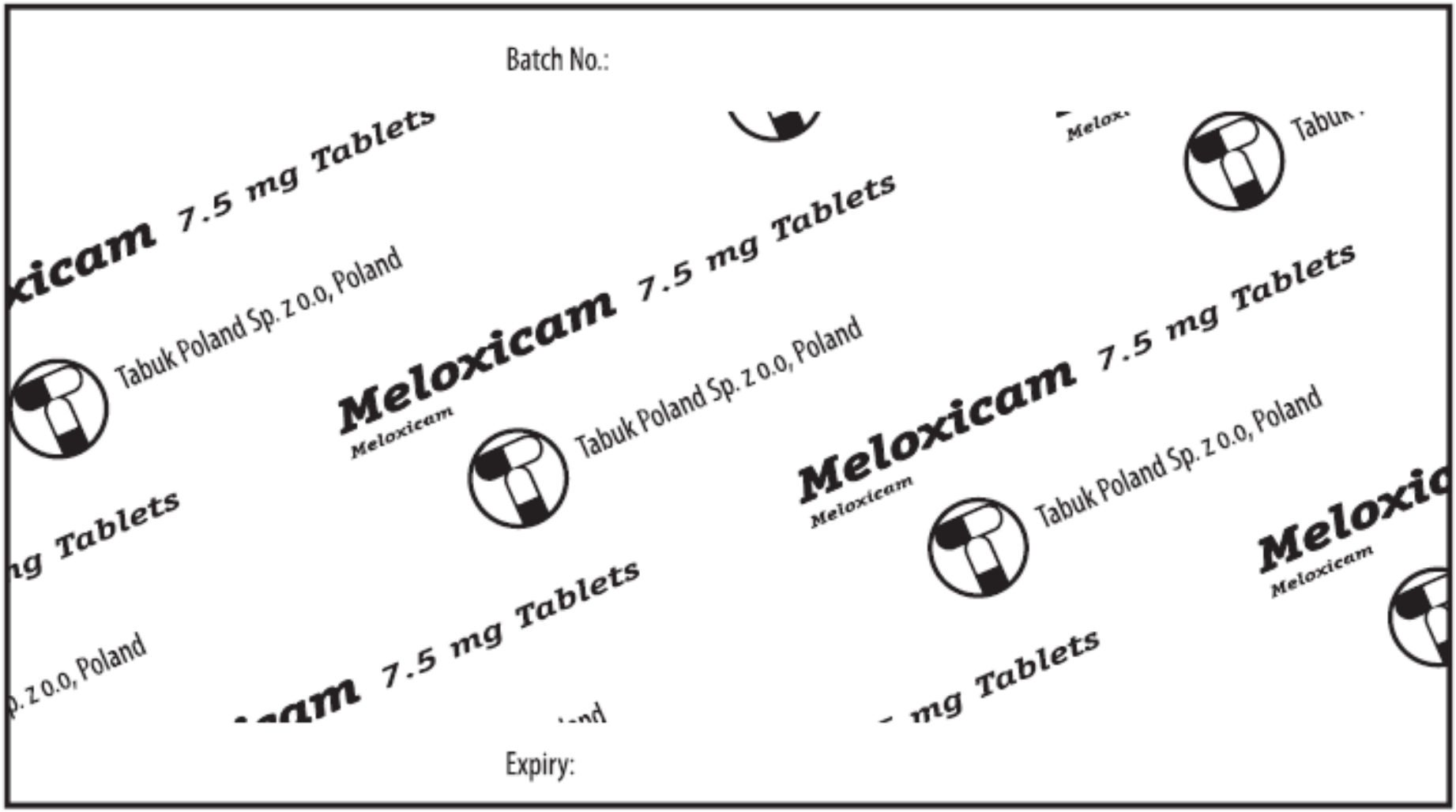
This medicinal product is authorised in the Member States of the EEA under the following names:
Czech Republic – Movmaks 7.5 mg tablety, Movmaks 15 mg tablety
Hungary – Movmax 7.5 mg tableta, Movmax 15 mg tableta
Poland – Movmax 7.5 mg, Movmax 15 mg
UK – Meloxicam 7.5 mg tablets, Meloxicam 15 mg tablets

This leaflet was last approved in: November 2008

Module 4
Labelling




30 tablets
Meloxicam 7.5 mg Tablets
BN:
EXP: mm/yyyy
POM
Each tablet contains 7.5 mg meloxicam.
Contains lactose.
See leaflet for further information.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
LA4074
Meloxicam 7.5 mg Tablets
30 tablets
Meloxicam 7.5 mg Tablets
Meloxicam 7.5 mg Tablets.
PL 30867/0001
Marketing authorisation holder:
Tabuk Poland Sp. z o.o.
ul. Capri 2/77, 02-762 Warsaw, Poland
Bar code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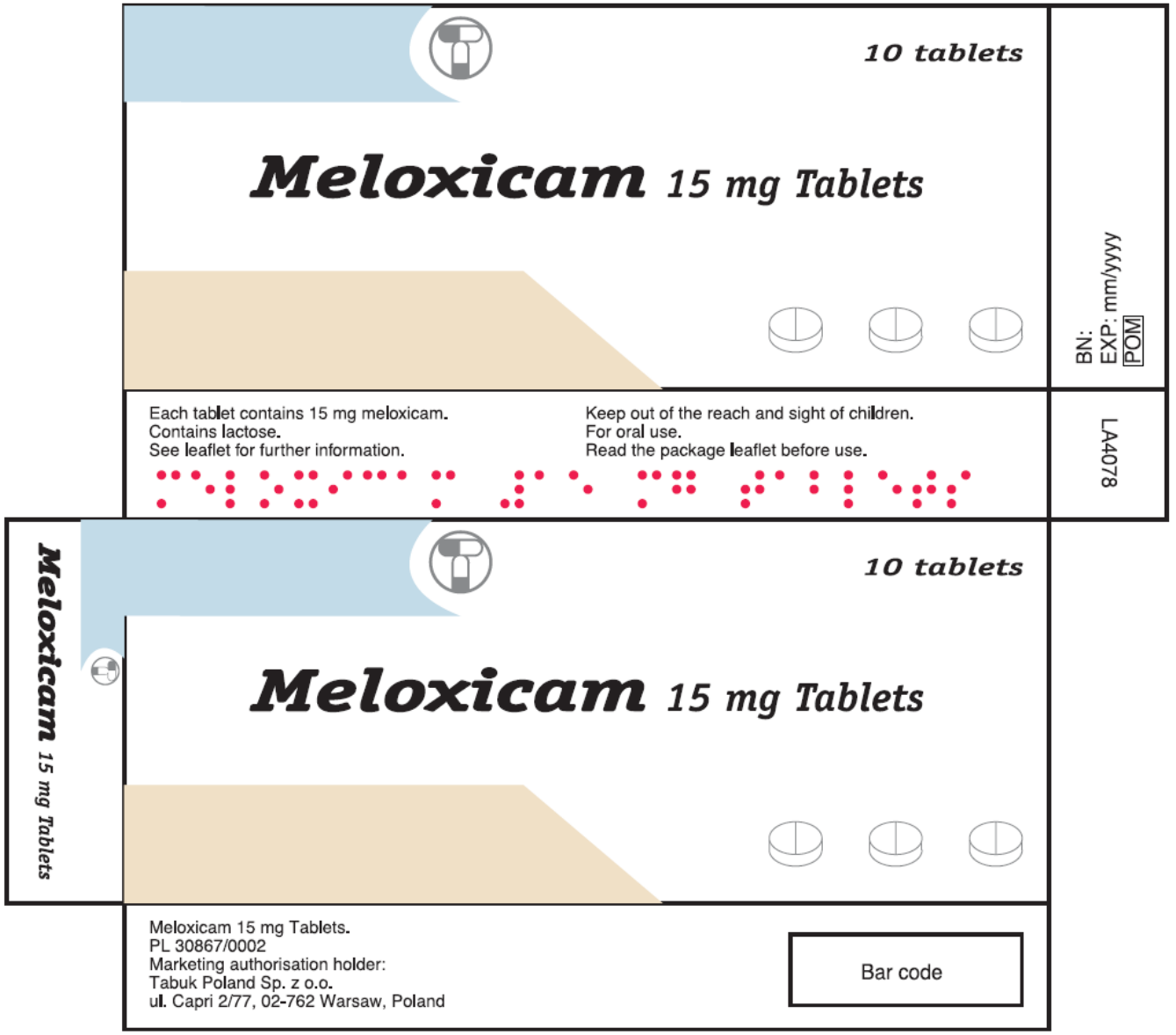
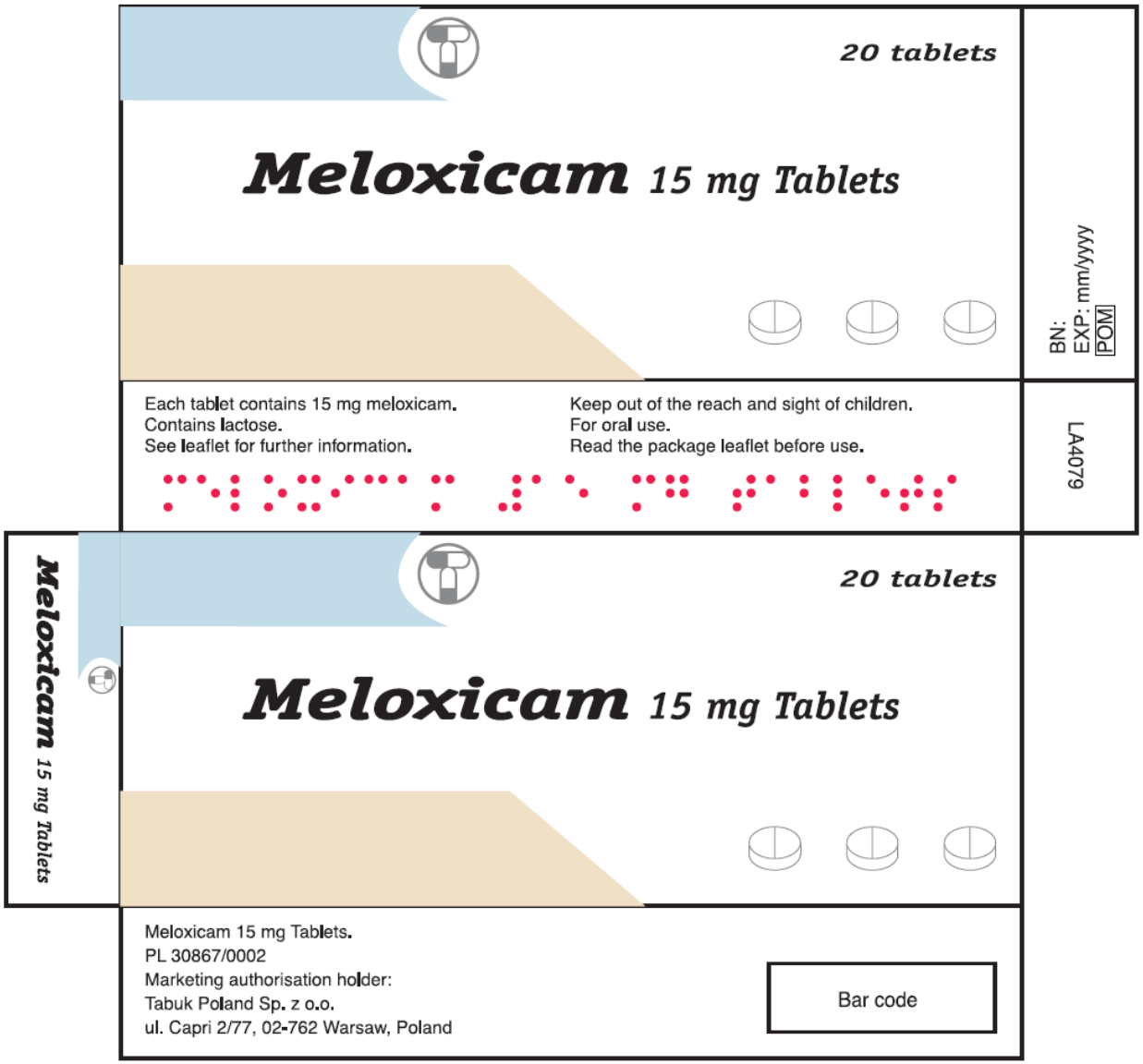
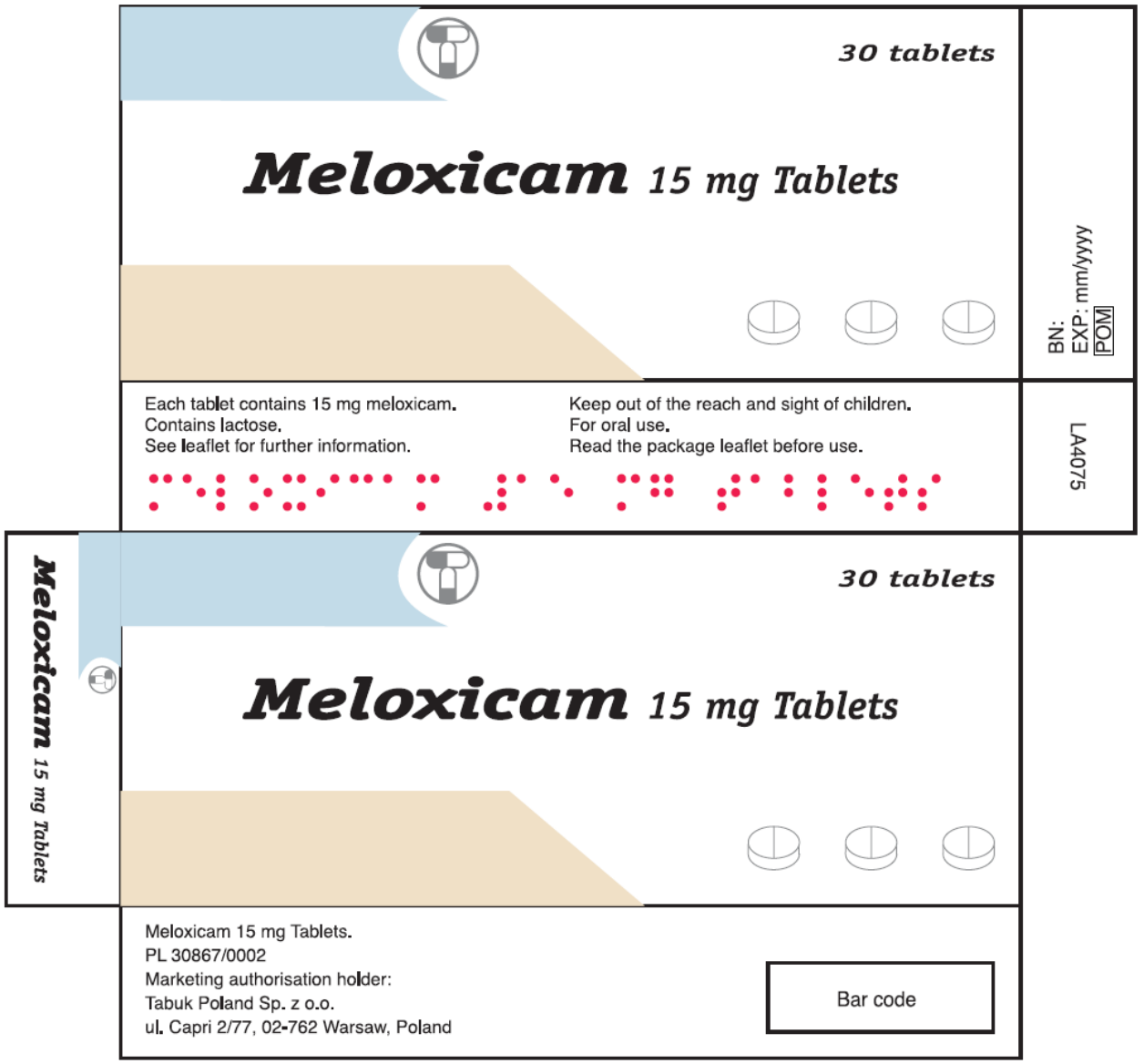
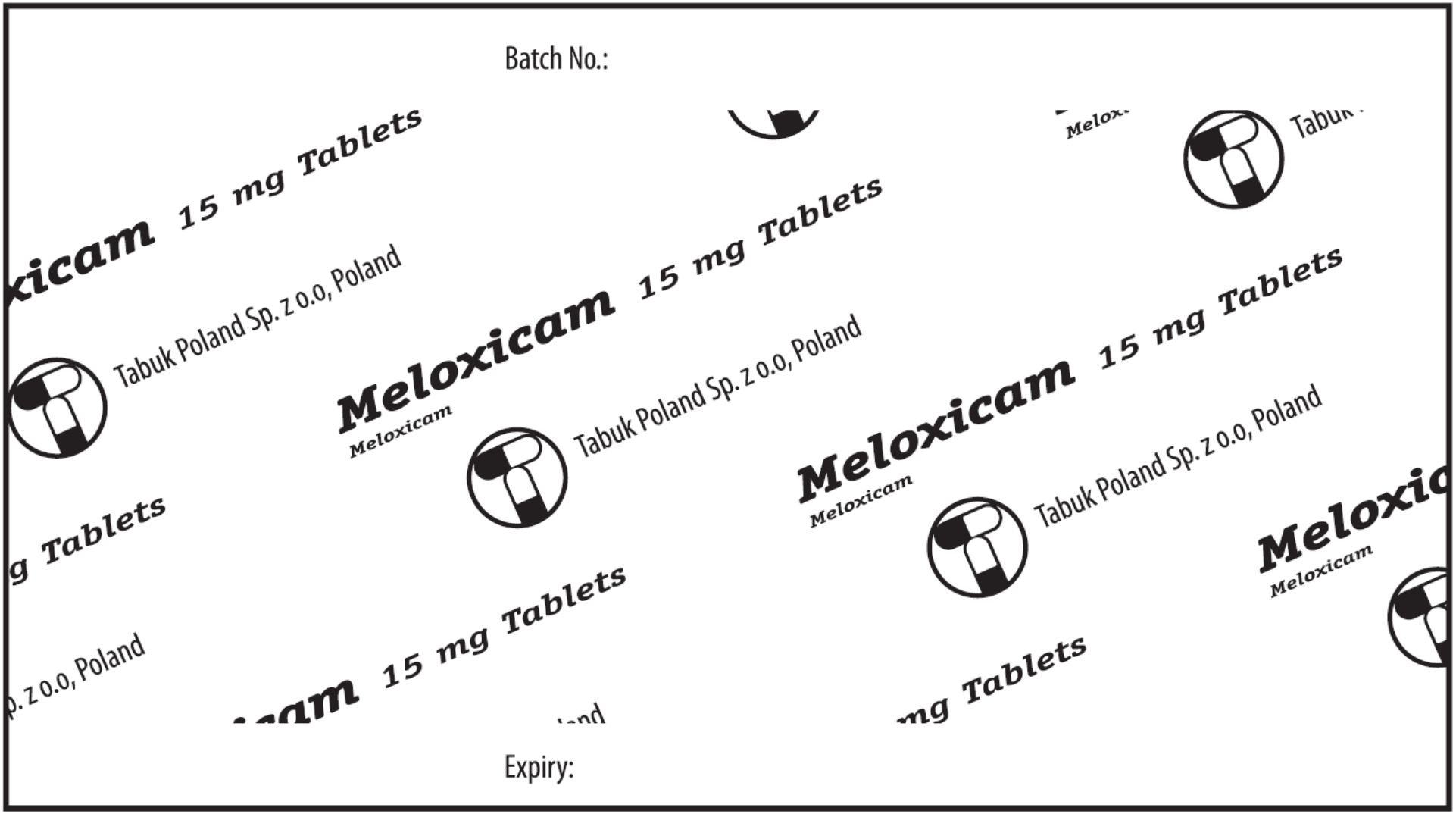
Meloxicam 7.5 mg Tablets
Tabuk Poland Sp. z o.o, Poland
Meloxicam
Expiry:


10 tablets
Meloxicam 15 mg Tablets
BN:
EXP: mm/yyyy
POM
Each tablet contains 15 mg meloxicam.
Contains lactose.
See leaflet for further information.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
LA4078
Meloxicam 15 mg Tablets
10 tablets
Meloxicam 15 mg Tablets
Meloxicam 15 mg Tablets.
PL 30867/0002
Marketing authorisation holder:
Tabuk Poland Sp. z o.o.
ul. Capri 2/77, 02-762 Warsaw, Poland
Bar code


20 tablets
Meloxicam 15 mg Tablets
BN:
EXP: mm/yyyy
POM
Each tablet contains 15 mg meloxicam.
Contains lactose.
See leaflet for further information.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
LA4079
Meloxicam 15 mg Tablets
20 tablets
Meloxicam 15 mg Tablets
Meloxicam 15 mg Tablets.
PL 30867/0002
Marketing authorisation holder:
Tabuk Poland Sp. z o.o.
ul. Capri 2/77, 02-762 Warsaw, Poland
Bar code


30 tablets
Meloxicam 15 mg Tablets
BN:
EXP: mm/yyyy
POM
Each tablet contains 15 mg meloxicam.
Contains lactose.
See leaflet for further information.
Keep out of the reach and sight of children.
For oral use.
Read the package leaflet before use.
LA4075
Meloxicam 15 mg Tablets
30 tablets
Meloxicam 15 mg Tablets
Meloxicam 15 mg Tablets.
PL 30867/0002
Marketing authorisation holder:
Tabuk Poland Sp. z o.o.
ul. Capri 2/77, 02-762 Warsaw, Poland
Bar code


Batch No.:
15 mg Tablets
Tabuk Poland Sp. z o.o, Poland
Meloxicam
Meloxicam
Expiry:

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 30867/0001-2; UK/H/1117/001-2/DC) could be approved. The products are prescription-only medicines for the short-term symptomatic 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) which were first authorised in France in 1995.

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.

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 Decentralised Procedure	UK/H/1117/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Hungary and Poland
Marketing Authorisation Number(s)	PL 30867/0001-2
Name and address of the authorisation holder	Tabuk Poland Sp. z.o.o, ul. Capri 2, lok. 77, 02-762 Warszawa, Poland

III SCIENTIFIC OVERVIEW AND DISCUSSION

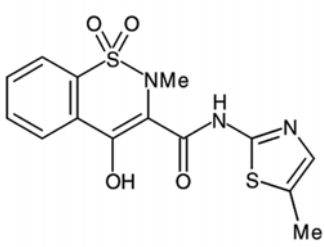
III.1 QUALITY ASPECTS

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, practically insoluble in water, slightly soluble in acetone,soluble in N, N-dimethylformamide, very slightly soluble in ethanol (96%) and in methanol.

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 microcrystalline cellulose, pregelatinised maize starch, lactose monohydrate, maize starch, sodium citrate dihydrate, 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, and that the preparation of lactose monohydrate is in accordance with the Public Statement (EMEA/CPMP/571/02). 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.

Comparable *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 specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
Both strengths of tablets are packaged polyvinylchloride/polyvinylidene chloride/aluminium blisters, which are contained in cardboard cartons. Pack sizes for both strengths are 7, 10, 14, 20, 30, 60 and 100 tablets. The marketing authorisation holder has stated that not all pack sizes are to be marketed, but has committed to submitting the packaging for any pack size to the regulatory authorities before marketing the product.

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 non-plasticised PVC materials for dry dosage forms for oral administration.

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 3 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

The pharmacological, pharmacokinetic and toxicological properties of meloxicam are well-known. As meloxicam is a well-known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review has been written by an appropriately qualified person and is satisfactory.

As the products are generic medicinal products intended to replace the originator products, it is not anticipated that they will increase the amount of active substance and their break-down products into the environment. For this reason, no environmental risk assessment has been submitted and none is required.

III.3 CLINICAL ASPECTS

Pharmacokinetics

To support the applications, the marketing authorisation holder has submitted one single-dose bioequivalence study.

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

Blood samples were taken pre- and up to 120 hours post dose. 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	37,358.0	39,557.8	1,538.3
Reference	36,949.7	38,732.0	1,287.5
Ratio (90% CI)	1.01 (0.96; 1.06)	1.02 (0.97; 1.08)	1.19 (1.13; 1.26)

The results proved the bioequivalence of both products with regards to both AUC values. However, the upper 90% confidence interval for C_{max} was marginally outside the upper range for bioequivalence. This was raised by the Reference Member State (RMS) in their Day 70 comments. In response, the marketing authorisation holder submitted the following arguments:

1. Meloxicam is a drug with a well-documented pharmacokinetic variability. C_{max} has been shown to be affected by age, gender and food intake. However, despite these effects, no impact of this has been reported on the efficacy and safety of meloxicam.
2. The small difference in C_{max} was considered to be due to one subject, who exhibited an abnormal laboratory result in the first period, which should have meant their data were excluded. Exclusion of this data would have brought the upper limit of C_{max} within the proposed confidence limit (1.24). The *Notes for Guidance on Bioequivalence (CPMP/EWP/QWP/1401/98) and the Q&A Document (EMEA/CHMP/EWP/40326/2006)* states that any justifications for widening the confidence intervals for C_{max} and exclusion of subjects from the final data should be pre-specified in the protocol. However, as the bioequivalence study was performed before this guidance was issued and conducted in-line with the guidance at the time, the justification is accepted.

On the basis of the information above, it was considered that the bioequivalence study could be accepted and bioequivalence could be considered to have been demonstrated between the test and reference products.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 15mg strength can be extrapolated to the 7.5mg strength tablets.

Efficacy

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

Safety
During the bioequivalence study, adverse events were reported in two subjects, acute rhinitis and tonsillitis. Both were considered to be not related to study drug.

Additional post marketing data supplied by the marketing authorisation holder confirm that the products are well-tolerated and safe for the intended use. No new or unexpected safety concerns have arisen from exposure to the finished products since their launch onto the EU market.

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 physician 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 15mg Tablets and the originator products Mobic 15mg Tablets (Boehringer Ingelheim Pharma Limited, UK).

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 15mg strength can be extrapolated to the 7.5mg strength tablets.

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 study supports 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 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome