Public Assessment Report

Meloxicam 7.5mg Orodispersible Tablets
Meloxicam 15mg Orodispersible Tablets

Meloxicam

PL 31388/0003
PL 31388/0004

Alpex Pharma (UK) Ltd

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Lay Summary

The MHRA granted Alpex Pharma (UK) Ltd Marketing Authorisations (licences) for the medicinal products Meloxicam Orodispersible Tablets 7.5mg (PL 31833/0003) and Meloxicam Orodispersible Tablets 15mg (PL 31833/0004) on 07/08/2009. The products are prescription only medicines.

The products contain the active ingredient meloxicam. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties. The approved indications in the UK, for Meloxicam, are short-term symptomatic treatment of exacerbations of osteoarthrosis; and long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

The products were demonstrated to be generic medical products of Mobic 15mg tablets, from the UK market, MA Holder Boehringer Ingelheim International GmbH, Germany.
Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Meloxicam Orodispersible Tablets 7.5mg (PL 31833/0003) and Meloxicam Orodispersible Tablets 15mg (PL 31833/0004) on 07/08/2009. The market authorisation holder is Alpex Pharma (UK) Ltd.

The application is according to Article 10(1) of 2001/83/EC, generic application, as amended. The reference product is Mobic 15mg tablets (Boehringer Ingelheim International GmbH, Germany) authorised in the UK, dated 21 Feb 1996 (PL 14598/0003). Bioequivalence has been established using Mobic 15mg tablets, from the UK market, MA Holder Boehringer Ingelheim International GmbH, Germany.

The products contain the active ingredient meloxicam. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties. The approved indications in the UK, for Meloxicam, are short-term symptomatic treatment of exacerbations of osteoarthrosis; and long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

GENERAL INFORMATION

Name: Meloxicam

![Structure of Meloxicam](image)

Description: Pale yellow to yellow powder.

Solubility: Practically insoluble in water, very slightly soluble in ethanol (96%) and in methanol, slightly soluble in acetone, soluble in DMF and in DMSO.

MW: 351.41
Polymorphism: Polymorphism exhibited. Form-1 is the desired form which is routinely manufactured via Dr Reddy’s manufacturing scheme.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active meloxicam is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated and support a retest period of 48 months with no specific storage conditions.

**DRUG PRODUCT**

**Other Ingredients.**
The other ingredients of the drug product are.

E 421: Mannitol
E 421: Mannitol pregranulated
E 420: Sorbitol
E 1201: Povidone Cl
E 330: Citric Acid monohydrate
E 951: Aspartame
E 553: Tale
E 572: Magnesium Stearate
E 1202: Povidone K30
E 572: Sodium Lauryl Sulphate
Yoghurt flavour
Forest fruit flavour

The excipients all comply with the requirements of the relevant Ph Eur monographs except for the Flavour yoghurt 503360 TP0551 and Flavour forest fruit 502874 AP0551. Appropriate details of composition, specification and analytical methods (generally in line with Ph Eur), and CoAs are provided for each flavour and accepted. Satisfactory TSE declarations for all excipients are provided and accepted.
Dissolution and impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packed in Al/Al blisters and HDPE bottles with desiccant insert. Satisfactory specifications and certificates of analysis are provided and accepted. Confirmation that the primary packaging components comply with the requirements of the Directive 2002/72/EC is provided and accepted.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 12 months with no specific storage conditions was approved.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided and none were required.
MEDICAL ASSESSMENT

Clinical Background
Meloxicam is a non-steroidal anti-inflammatory drug of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties (ATC code: M01 AC06).

The anti-inflammatory activity of Meloxicam is proven, though the exact mechanism is not known. There is at least one common mode of action shared by all NSAID (including Meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

The approved indications in the UK, for Meloxicam, are short-term symptomatic treatment of exacerbations of osteoarthritis; and long term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

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. 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. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

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.

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. 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.

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

Neither hepatic, nor mild and moderate renal insufficiencies 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.
Bioequivalence Study
The applicant has submitted results of a Comparative, Randomised, Single-Dose, 2-way Crossover Bioavailability Study of Alpex Meloxicam 15 mg Orally Disintegrating Tablets and Boehringer Ingelheim (Mobic®) Meloxicam 15 mg Tablets in Healthy Adult Volunteers under Fasting Conditions.

The applicant states that, “This study was conducted in compliance with the Good Laboratory Practice (GLP) and the International Conference on Harmonisation (ICH) harmonized tripartite guideline regarding Good Clinical Practice (GCP).

The study was conducted as an open-labelled, randomised, 2-way crossover, 2-sequence, comparative bioavailability study under fasting conditions. The primary objective was to assess the single-dose relative bioavailability of Alpex Meloxicam 15 mg Orally Disintegrating tablets (ODT) and Boehringer Ingelheim (Mobic®) Meloxicam 15 mg tablets in healthy adult volunteers under fasting conditions.

Twenty-eight healthy adult subjects (27 males and 1 female) were randomized and twenty six subjects (25 males and 1 female) completed both periods of the study. Subjects 16 and 22 were excluded from the pharmacokinetic and statistical analysis because they did not complete the clinical phase of the study. Subject 16 was dropped after the 4 hours’ post dosing blood sampling in Period 2, due to misconduct. Subject 22 did not return for the 2nd period of the study.

Subjects randomized to the test product received a single oral 15 mg dose of Meloxicam ODT, placed between the tongue and the palate and allowed to disintegrate. The tablet was not chewed or swallowed until it had disintegrated. After 5 minutes, 240 ml of water was administered. Subjects randomized to the reference therapy received a single oral dose of Mobic® (Meloxicam) 15mg tablet taken with 240mL of water.

The study states that the 90% confidence intervals of the ratios of least-squares means for the log-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax of the test to reference formulation were to be within 0.80 to 1.25.

Blood samples (1 x 3 ml) were collected in blood collection tubes containing EDTA before dosing and at the following times thereafter: 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours. The plasma samples were analysed using the LC/MS/MS method, with a validated range of assay of 10-2000 ng/ml.

Results
The mean Meloxicam Plasma concentration/time curves obtained after administration of the two formulations are reported in the figures below:
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Product</th>
<th>AUC 0-t (± SD) (ng·h/mL)</th>
<th>AUCinf (± SD) (ng·h/mL)</th>
<th>AUC/AUCinf (%)</th>
<th>Cmax (± SD) (ng/mL)</th>
<th>tmax (h)</th>
<th>kel (1/h)</th>
<th>t1/2 (h)</th>
</tr>
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<tbody>
<tr>
<td>Meloxicam ODT 15mg</td>
<td>49937 (±13084)</td>
<td>54421 (±18882)</td>
<td>93.6</td>
<td>1637 (±233)</td>
<td>3.75</td>
<td>0.0340</td>
<td>22.9</td>
</tr>
<tr>
<td>Mobic® (Meloxicam) 15mg Tablet</td>
<td>49196 (±14118)</td>
<td>54431 (±21465)</td>
<td>92.9</td>
<td>1443 (±259)</td>
<td>4.77</td>
<td>0.0334</td>
<td>23.7</td>
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There are statistically significant sequence and formulation effects. However, the adequacy of the washout period has been accepted and the 90% confidence interval and the ratio of the test to the reference formulations fall within the 0.80-1.25 acceptance range for bioequivalence. Bioequivalence has, therefore been demonstrated. Given that linear kinetics apply between the 15mg and 7.5mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 7.5mg tablets is not considered necessary.

**Efficacy**
Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

**Safety**
Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

**Expert Report**
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

**Summary Of Product Characteristics**
This is satisfactory.

**Patient Information Leaflet**
This is satisfactory.

**Conclusions**
The applicant has demonstrated bioequivalence. Marketing authorisations should be granted for these products.
Overall Conclusion and Risk/Benefit Analysis

**Quality**
The important quality characteristics of Meloxicam Orodispersible Tablets 7.5mg and Meloxicam Orodispersible Tablets 15mg 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 benefit/risk balance.

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

**Clinical**
Bioequivalence has been demonstrated between the applicant’s Meloxicam Orodispersible Tablets 15mg and the reference product. Given that linear kinetics apply between the 15mg and 7.5mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 7.5mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Mobic 7.5mg and 15mg Tablets.

**Risk/Benefit Analysis**
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. The risk benefit is, therefore, considered to be positive.
Steps Taken During Assessment

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<tr>
<td>1</td>
<td>The MHRA received the application on 21/11/2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 05/01/2009.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 03/03/2009 and on the clinical assessment on 27/04/2009, 01/07/2009 and 22/07/2009.</td>
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<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 26/03/2009 and on the clinical assessment on 26/05/2009, 14/07/2009 and 30/07/09.</td>
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<tr>
<td>5</td>
<td>The application was determined on 07/08/2009.</td>
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Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Meloxicam 7.5 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Meloxicam 7.5 mg
For Excipients See 6.1.

3 PHARMACEUTICAL FORM
Orodispersible Tablets
Round light yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Short-Term Symptomatic Treatment of Exacerbations of Osteoarthrosis.
Long Term Symptomatic Treatment of Rheumatoid Arthritis or Ankylosing Spondylitis.

4.2 Posology and method of administration
Oral Use
• Exacerbations of Osteoarthrosis: 7.5 mg/day (one 7.5 mg tablet); if necessary, in
the absence of improvement, the dose may be increased to 15 mg/day (two 7.5 mg tablets).
- Rheumatoid arthritis, Ankylosing Spondylitis: 15 mg/day (two 7.5 mg tablets).

(See also 'Special Populations')

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

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.

DO NOT EXCEED THE DOSE OF 15 MG/DAY.

Meloxicam Orodispersible Tablets should be placed in the mouth on the tongue and allowed to dissolve slowly for five minutes (the tablet should not be chewed and should not be swallowed undissolved), before swallowing with a drink of 240 ml of water.
Water may be used to moisten the buccal mucosa in patients with a dry mouth.

Special Populations

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

Renal impairment (see section 5.2):

In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day.
No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see section 4.3).

Hepatic Impairment (See Section 5.2):

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

Children and adolescents:

Meloxicam Orodispersible Tablets is contraindicated in children and adolescents aged under 16 years (see section 4.3).
4.3 Contraindications

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

- Third trimester of pregnancy (see section 4.6 ‘Pregnancy and lactation’);
- Children and adolescents aged under 16 years;
- Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs;
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- Severely impaired liver function;
- Non-dialysed severe renal failure;
- Gastrointestinal bleeding, 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).

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 Orodispersible Tablets with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

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

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

Gastrointestinal effects

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as curative treatment or given in geriatrics, anticoagulants such as warfarin, or other non steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount)(see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 – 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 monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with Meloxicam Orodispersible Tablets.

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 orodispersible tablets 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.

**Parameters of liver and renal function**

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

The dose of Meloxicam in patients with end-stage renal failure on haemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min).

Sodium, potassium and water retention

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

Hyperkalaemia

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase 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 orodispersible tablet, as any other NSAID may mask symptoms of an underlying infectious disease.

The use of meloxicam orodispersible tablet, 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.

Meloxicam orodispersible tablet contains a source of phenylalanine: Aspartame (E951) and may be harmful for people with phenylketonuria.

Meloxicam orodispersible tablet contains Sorbitol (E420): Patients with rare hereditary problems of fructose intolerance should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Pharmacodynamic Interactions:

*Other non steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid ≥ 3g/d:*
combination (see section 4.4) with other non steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥3g as total daily amount) is not recommended.

*Corticosteroids (e.g. Glucocorticoids):*

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

*Anticoagulant or heparin administered in geriatrics or at curative doses:*

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

In remaining cases of heparin use caution is necessary due to an increased bleeding risk. Careful monitoring of the INR is required if it proves impossible to avoid such combination.

*Thrombolytics and antiplatelet drugs:*

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).

*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 antihypertensive drugs (e.g. Beta-blockers):*

As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

*Calcineurin inhibitors (e.g. cyclosporin, tacrolimus):*

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:*

NSAIDs have been reported to decrease the efficacy of intrauterine devices.

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

*Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs)*

*Lithium:*

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

*Methotrexate:*

NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended (see section 4.4).
The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

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

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)

Cholestyramine:

Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.

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 oligohydroamnios;

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 therefore is not recommended in women who are breastfeeding.

4.7 Effects on ability to drive and use machines

There are no specific studies on the ability to drive and use machinery. 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

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

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

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

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:

Very common ( > 1/10); common ( > 1/100, < 1/10); uncommon ( > 1/1000, < 1/100); rare ( > 1/10000, < 1/1000); very rare ( < 1/10000)

b) Table of adverse reactions

**Blood and lymphatic system disorders**

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia</td>
</tr>
</tbody>
</table>

Very rare cases of agranulocytosis have been reported (see section c).

**Immune system disorders**

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Allergic reactions other than anaphylactic or anaphylactoid reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known:</td>
<td>Anaphylactic reaction, anaphylactoid reaction</td>
</tr>
</tbody>
</table>

**Psychiatric disorders**

<table>
<thead>
<tr>
<th>Rare:</th>
<th>Mood altered, nightmares</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known:</td>
<td>Confusional state, disorientation</td>
</tr>
</tbody>
</table>
### Nervous system disorders

<table>
<thead>
<tr>
<th>Common:</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon:</td>
<td>Dizziness, somnolence</td>
</tr>
</tbody>
</table>

### Eye disorders

<table>
<thead>
<tr>
<th>Rare:</th>
<th>Visual disturbance including vision blurred; conjunctivitis</th>
</tr>
</thead>
</table>

### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Vertigo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Tinnitus</td>
</tr>
</tbody>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Rare:</th>
<th>Palpitations</th>
</tr>
</thead>
</table>

Cardiac failure has been reported in association with NSAID treatment.

### Vascular disorders

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Blood pressure increased (see section 4.4), flushing</th>
</tr>
</thead>
</table>

### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Rare:</th>
<th>Asthma in individuals allergic to aspirin or other NSAIDs</th>
</tr>
</thead>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Very common:</th>
<th>Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon:</td>
<td>Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation</td>
</tr>
<tr>
<td>Rare:</td>
<td>Colitis, gastroduodenal ulcer, oesophagitis</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Gastrointestinal perforation</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Liver function disorder (e.g. raised transaminases or bilirubin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Angioedema, pruritus, rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Dermatitis bullous, erythema multiforme</td>
</tr>
<tr>
<td>Not known:</td>
<td>Photosensitivity reaction</td>
</tr>
</tbody>
</table>

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Sodium and water retention, hyperkalaemia (see section 4.4. Special warnings and special precautions for use and section 4.5.), renal function test abnormal (increased serum creatinine and/or serum urea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Acute renal failure in particular in patients with risk factors (see section 4.4.)</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Oedema including oedema of the lower limbs.</th>
</tr>
</thead>
</table>

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

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

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

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

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non steroidal anti-inflammatory agents, oxicams

ATC code: M01 AC06

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 NSAID, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAID (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 achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).
With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/ml for 7.5 mg doses and 0.8 - 2.0 µg/ml for 15 mg doses, respectively (cmin and cmax at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

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

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

**Elimination**
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine. The mean elimination half-life is about 20 hours. Total plasma clearance amounts on average 8 mL/min.

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

**Special populations**

*Hepatic/renal insufficiency:*
Neither hepatic, nor mild nor moderate renal insufficiency has 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 NSAID: Gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits.

The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on a mg/kg dose basis (75 kg person). Fetal toxic 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

- E 421: Mannitol
- E 421: Mannitol pregranulated
- E 420: Sorbitol
- E 1201: Povidone Cl
- E 330: Citric Acid monohydrate
- E 951: Aspartame
- E 553: Talc
- E 572: Magnesium Stearate
- E 1202: Povidone K30
- E 572: Sodium Lauryl Sulphate
- Yoghurt flavour
- Forest fruit flavour

#### 6.2 Incompatibilities

Not applicable
6.3 Shelf life

1 year

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Boxes containing 3 aluminium blister packs of 10 tablet each.
Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 30 tablets each.
Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 200 tablets each.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alpex Pharma (UK) Limited,
Yew Tree Lodge,
Southill, Biggleswade,
Beds. SG 18 9 LP.

8 MARKETING AUTHORISATION NUMBER(S)

PL 31388/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/08/2009

10 DATE OF REVISION OF THE TEXT

07/08/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Meloxicam 15 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meloxicam 15 mg
For Excipients See 6.1.

3 PHARMACEUTICAL FORM

Orodispersible Tablets
Round light yellow scored tablet, which can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-Term Symptomatic Treatment of Exacerbations of Osteoarthritis.

Long Term Symptomatic Treatment of Rheumatoid Arthritis or Ankylosing Spondylitis.

4.2 Posology and method of administration

Oral Use

- Exacerbations of Osteoarthritis: 7.5 mg/day (half a 15 mg tablet); if necessary, in the absence of improvement, the dose may be increased to 15 mg/day.
- Rheumatoid arthritis, Ankylosing Spondylitis: 15 mg/day (one 15mg tablets).
According to the therapeutic response, the dose may be reduced to 7.5 mg/day (one 7.5 mg tablet).

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.

DO NOT EXCEED THE DOSE OF 15 MG/DAY.

Meloxicam Orodispersible Tablets should be placed in the mouth on the tongue and allowed to dissolve slowly for five minutes (the tablet should not be chewed and should not be swallowed undissolved), before swallowing with a drink of 240 ml of water.

Water may be used to moisten the buccal mucosa in patients with a dry mouth.

Special Populations

Elderly patients and patients with increased risks for adverse reaction (see section 5.2):

The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day (half a 15mg Tablet). 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 (half a 15mg Tablet).

No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see section 4.3).

Hepatic Impairment (See Section 5.2):

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

Children and adolescents:

Meloxicam Orodispersible Tablets is contraindicated in children and adolescents aged under 16 years (see section 4.3).

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

- Third trimester of pregnancy (see section 4.6 ‘Pregnancy and lactation’);
- Children and adolescents aged under 16 years;
- Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs;
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy;
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- Severely impaired liver function;
- Non-dialysed severe renal failure;
- Gastrointestinal bleeding, 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).

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 Orodispersible Tablets with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

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

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

Gastrointestinal effects

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

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

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as curative treatment or given in geriatrics, anticoagulants such as warfarin, or other nonsteroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses ($\geq 1g$ as single intake or $\geq 3g$ as total daily amount)(see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 – 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 monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with Meloxicam Orodispersible Tablets.

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 orodispensible tablets 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.

Parameters of liver and renal function

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen 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.
The dose of Meloxicam in patients with end-stage renal failure on haemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min).

**Sodium, potassium and water retention**

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

**Hyperkalaemia**

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase 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 orodispersible tablet, as any other NSAID may mask symptoms of an underlying infectious disease.

The use of meloxicam orodispersible tablet, 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.

Meloxicam orodispersible tablet contains a source of phenylalanine: Aspartame (E951) and may be harmful for people with phenylketonuria.

Meloxicam orodispersible tablet contains Sorbitol (E420): Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

Interaction studies have only been performed in adults.

**Pharmacodynamic Interactions:**

*Other non steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid ≥ 3g/d:*
combination (see section 4.4) with other non steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount) is not recommended.

*Corticosteroids (e.g. Glucocorticoids):*

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

*Anticoagulant or heparin administered in geriatrics or at curative doses:*

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

In remaining cases of heparin use caution is necessary due to an increased bleeding risk. Careful monitoring of the INR is required if it proves impossible to avoid such combination.

*Thrombolytics and antiplatelet drugs:*

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).

*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 cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).
Other antihypertensive drugs (e.g. Beta-blockers):

As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Calcineurin inhibitors (e.g. cyclosporin, tacrolimus):

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:

NSAIDs have been reported to decrease the efficacy of intrauterine devices.

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

Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs)

Lithium:

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

Methotrexate:

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

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

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

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)

*Cholestyramine:*

Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs. This interaction is of clinical significance.

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 oligohydroamniosis;

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 therefore is not recommended in women who are breastfeeding.

4.7 Effects on ability to drive and use machines

There are no specific studies on the ability to drive and use machinery. 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

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

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

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

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:

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (> 1/10000, < 1/1000); very rare (< 1/10000)

b) Table of adverse reactions

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Uncommon:</th>
<th>Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia</td>
</tr>
</tbody>
</table>

Very rare cases of agranulocytosis have been reported (see section c).

Immune system disorders

| Uncommon: | Allergic reactions other than anaphylactic or anaphylactoid reactions |
| Not known: | Anaphylactic reaction, anaphylactoid reaction |

Psychiatric disorders

| Rare: | Mood altered, nightmares |
| Not known: | Confusional state, disorientation |

Nervous system disorders

| Common: | Headache |
| Uncommon: | Dizziness, somnolence |
Eye disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Visual disturbance including vision blurred; conjunctivitis</td>
</tr>
</tbody>
</table>

Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Rare</td>
<td>Tinnitus</td>
</tr>
</tbody>
</table>

Cardiac disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Palpitations</td>
</tr>
</tbody>
</table>

Cardiac failure has been reported in association with NSAID treatment.

Vascular disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Blood pressure increased (see section 4.4), flushing</td>
</tr>
</tbody>
</table>

Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Asthma in individuals allergic to aspirin or other NSAIDs</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation</td>
</tr>
<tr>
<td>Rare</td>
<td>Colitis, gastroduodenal ulcer, oesophagitis</td>
</tr>
<tr>
<td>Very rare</td>
<td>Gastrointestinal perforation</td>
</tr>
</tbody>
</table>

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

Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Liver function disorder (e.g. raised transaminases or bilirubin)</td>
</tr>
</tbody>
</table>
Very rare: Hepatitis

Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Angioedema, pruritus, rash</td>
</tr>
<tr>
<td>Rare</td>
<td>Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria</td>
</tr>
<tr>
<td>Very rare</td>
<td>Dermatitis bullous, erythema multiforme</td>
</tr>
<tr>
<td>Not known</td>
<td>Photosensitivity reaction</td>
</tr>
</tbody>
</table>

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Sodium and water retention, hyperkalaemia (see section 4.4. Special warnings and special precautions for use and section 4.5.), renal function test abnormal (increased serum creatinine and/or serum urea)</td>
</tr>
<tr>
<td>Very rare</td>
<td>Acute renal failure in particular in patients with risk factors (see section 4.4.)</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Oedema including oedema of the lower limbs.</td>
</tr>
</tbody>
</table>

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

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

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

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

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non steroidal anti-inflammatory agents, oxicams

ATC code: M01 AC06

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 NSAID, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAID (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 achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small
peak-trough fluctuation in the range of 0.4 - 1.0 µg/ml for 7.5 mg doses and 0.8 - 2.0 µg/ml for 15 mg doses, respectively (cmin and cmax at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

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

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

**Elimination**
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine. The mean elimination half-life is about 20 hours. Total plasma clearance amounts on average 8 mL/min.

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

**Special populations**

**Hepatic/renal insufficiency:**
Neither hepatic, nor mild nor moderate renal insufficiency has 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 NSAID: Gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits.

The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on a mg/kg dose basis (75 kg person). Foetotoxic 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

- E 421: Mannitol
- E 421: Mannitol pregranulated
- E 420: Sorbitol
- E 1201: Povidone CI
- E 330: Citric Acid monohydrate
- E 951: Aspartame
- E 553: Talc
- E 572: Magnesium Stearate
- E 1202: Povidone K30
- E 572: Sodium Lauryl Sulphate
- Yoghurt flavour
- Forest fruit flavour

6.2 Incompatibilities

Not applicable
6.3 Shelf life

1 year

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Boxes containing 3 aluminium blister packs of 10 tablet each (30 total tablets).
Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 30 tablets each.
Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 200 tablets each.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alpex Pharma (UK) Limited,
Yew Tree Lodge,
Southill, Biggleswade,
Beds. SG 18 9 LP.

8 MARKETING AUTHORISATION NUMBER(S)

PL 31388/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/08/2009

10 DATE OF REVISION OF THE TEXT

07/08/2009
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 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 become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1 WHAT MELOXICAM ORODISPERSM TABLETS ARE AND WHAT THEY ARE USED FOR

Meloxicam tablets belong to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which can be used to relieve inflammation and pain in joints and muscles. (Oral dispersible tablets are tablets which dissolve easily in the mouth.)

Meloxicam tablets are used for:
- the short-term treatment of the symptoms of acute attacks of osteoarthritis;
- the long-term treatment of the symptoms of:
  - rheumatoid arthritis;
  - ankylosing spondylitis (a disease of the backbone).

2 BEFORE YOU TAKE MELOXICAM TABLETS

Do not take Meloxicam tablets and tell your doctor if you:
- are allergic to Meloxicam or to any of the other ingredients (see section 8 for a list of these);
- are pregnant, planning to become pregnant or if you are breastfeeding;
- are allergic to aspirin or to other non-steroidal anti-inflammatory medicines (NSAIDs);
- have ever developed signs of asthma (wheezing), nasal polyps along with a runny nose, swelling of the skin or rashes when taking aspirin or other anti-inflammatory medicines;
- have or have ever had an ulcer of the stomach or intestine;
- have had any kind of bleeding disorder or have ever suffered from bleeding in the stomach or intestine or bleeding in the brain;
- have severe liver disease;
- have severe kidney failure and are not receiving dialysis;
- have ever had a facial rash or angioedema (swelling of tissues);
- suffer from severe heart failure.

If you think any of these apply to you, do not start taking these Meloxicam tablets. Talk to your doctor first and follow the advice given to you.

Take special care with Meloxicam tablets:
- If you have a history of inflammation of the stomach or gut, or any other gastrointestinal disease e.g. ulcerative colitis or Crohn’s disease;
- If you have high blood pressure;
- If you have heart, liver or kidney disease;
- If you are diabetic;
- If you are elderly (65 years old or more);
- If you have an inherited illness called phenylketonuria, because this medicine contains aspartame (E951).

If you have been told that you have intolerance to some sugars, because this medicine contains sorbitol (E420), a kind of sugar;

- If you have a reduced volume of blood in your body, which may occur if you have serious blood loss or burns, surgery or low fluid intake;
- If you have ever been diagnosed with high potassium levels in the blood.

Tell your doctor if you think any of these apply to you.

Warning

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

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

Discuss your treatment with your doctor or pharmacist if you have heart problems, have previously had a stroke or you think you might be at risk of conditions such as high blood pressure, diabetes or high cholesterol, or if you are a smoker.

Taking other medicines

When you are taking Meloxicam tablets, do not take any other medicines – including medicines obtained without a prescription – without talking to your doctor or pharmacist.

- Tell your doctor or pharmacist if you are taking any of the following medicines:
  - any other non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin;
  - medicines to prevent blood clotting, such as warfarin, heparin;
  - medicines to break down blood clots;
  - medicines to treat high blood pressure;
  - oral contraceptives;
  - cyclosporin;
  - any diuretic medicine (your doctor may monitor your kidney function if you are taking diuretics);
  - insulin, used to treat medical disorders;
  - selective serotonin re-uptake inhibitors, used in the treatment of depression;
  - antidepressants;
  - osteoporosis;
  - you use an intrauterine contraceptive device (IUD), usually known as a coil.

Pregnancy and breast-feeding

Meloxicam tablets are not recommended for use by women who are pregnant or breastfeeding.

Tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are breastfeeding.

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

Children and adolescents (under 10 years old)

This medicine should not be given to children under 10 years old.

Driving and using machinery

Do not drive or operate machinery until you know how Meloxicam tablets affect you. If the tablets make you feel light-headed, dizzy or drowsy, or cause blurred vision, do not drive or operate machinery.

Important information about some of the ingredients of Meloxicam tablets:
- These tablets contain the sweetener aspartame (E951), a source of phenylalanine. Contact your doctor before taking them if you have an inherited illness called phenylketonuria.
- These tablets contain sorbitol (E420), a kind of sugar. If you have ever been told you have intolerance to some sugars, contact your doctor before taking these tablets.

3 HOW TO TAKE MELOXICAM TABLETS

Always take Meloxicam tablets exactly as your doctor has told you to. Do not exceed the recommended dose or duration of treatment.

Read the leaflet carefully.
Taking this medicine

- Place the tablet in your mouth on your tongue.
- Allow it to dissolve, slowly for five minutes (it must never be chewed or swallowed undissolved).
- Swallow with a drink of 240 ml of water.
- If you have a dry mouth, use water to moisten it first.
- Never take more than the recommended maximum dose of 15 mg (two tablets) a day.

Dosage

The dose depends on the medical condition which is being treated. Your doctor will let you know how much you should take.

For the treatment of acute attacks of osteoarthritis:

The usual dose is 7.5 mg (one tablet) a day. Your doctor may increase your dose to 15 mg (two tablets) a day if necessary.

For the treatment of rheumatoid arthritis and ankylosing spondylitis:

The usual dose is 15 mg (two tablets) a day. Your doctor may reduce your dose to 7.5 mg (one tablet) a day if necessary.

If you have any of the conditions listed in Section 2 under the heading “Take special care with Meloxicam tablets,” your doctor may restrict your dose to 7.5 mg (one tablet) a day.

If you feel that the effect of these Meloxicam tablets is too strong or too weak, or after several doses you do not feel any improvement in your condition, consult your doctor or pharmacist.

If you take more of this medicine than you should

Contact your doctor or pharmacist immediately or go immediately to the accident and emergency department of your nearest hospital, taking this leaflet or the tablets with you.

If you forget to take your tablet

Never take more tablets on the same day to make up for the tablets you have missed. Take your usual dose the next day.

4. POSSIBLE SIDE EFFECTS

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

- If you have a history of gastrointestinal symptoms while taking anti-inflammatory drugs, your doctor may monitor your progress while you are having this treatment.
- Clinical trials and scientific 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 bleeding in the arteries (which could, for example, lead to heart attack or stroke).

Contact your doctor immediately, or go immediately to the accident and emergency department of your nearest hospital, taking this leaflet or the tablets with you, if you get the following serious side effects:

- Severe allergic reactions which may include breathing difficulties, skin reactions and asthma attacks (common side effects, affecting less than 1 person in 10);
- Bleeding in the stomach or intestine, or peptic ulcers, soreness or inflammation of the mouth, or inflammation of the gut (uncommon side effects, affecting less than 1 person in 100);
- Severe blurring or peeling of the skin, swelling around the eyes, lips and face, caused by exposure to sunlight (rare side effects, affecting less than 1 person in 1,000).

Contact your doctor if you get the following side effects:

- Common side effects (affecting less than 1 person in 10):
  - Indigestion, feeling or being sick, abdominal pain, constipation, diarrhoea, skin rash or itching;
  - Light-headedness, headaches;
- Uncommon side effects (affecting less than 1 person in 100):
  - Anaemia;
  - Nettle rash or hives, pruritis;
  - Dizziness, drowsiness;
  - Irregular heart beat, increased blood pressure, hot flushes;
  - Changes to liver function;
  - Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis;
  - Salt and water retention, excessive potassium, changes to kidney function, swelling of ankles and legs.

Rare side effects (affecting less than 1 person in 1,000):

- Abnormal white blood cell or platelet numbers;
- A hole in the bowel wall, inflammation or sores of the stomach or intestine (ulcers of the stomach or intestine);
- Bleeding and perforations in the stomach or intestine could occur at any time, and can sometimes, especially in the elderly, be severe and could, very rarely, if ever, be fatal; at least 1 in every 10,000 patients treated, be fatal;
- Flushing;
- Mood swings, tinnitus, insomnia, nightmares;
- Visual disturbances such as blurred vision;
- Infarction of the liver (hepatitis);
- Kidney failure.

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 store the tablets in an open container.
- This product does not require any other special storage requirements in Europe.
- Do not use Meloxicam 7.5 mg orodispersible tablets after the expiry date, which is stated on the pack. The expiry date refers to the last day of that month.
- Return all unused medicines to your pharmacist for safe disposal.

6. FURTHER INFORMATION

What Meloxicam 7.5 mg orodispersible tablets contain

The active ingredient is Meloxicam. Each tablet contains 7.5 mg of Meloxicam. The other ingredients are mannitol (E421), aspartame (E951), sodium citrate (E331), citric acid (E330), yoghurt flavour and fruit extract, the tablets are coated with an enteric coating (E553), sodium lauryl sulphate and magnesium stearate (E572).

What Meloxicam tablets look like and contents of the pack

Meloxicam 7.5 mg tablets are brown, light yellow in colour. The tablets are supplied in:

- Boxes containing 3 blister packs of 10 tablets each;
- Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 30 tablets each
- Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 200 tablets each.

Marketing Authorisation Holder

The Marketing Authorisation Holders:

Alphex Pharma (UK) Limited,
Yew Tree Lodge,
Southall,
Bilgraves Lane,
SU18 9LP

UK

Tel: 01442-817500
Fax: 01442-817600

Medical Information Direct Line: +44 (0) 1476 570819
Medical Information Facsimile: +44 (0) 1476 856617
Medical Information e-mail: care@alphexpharmablock.co.uk

Manufacturer

Alphex Pharma SA,
Via Carbonale,
CH 6900 Muzzoico,
Switzerland

This leaflet was last approved in 06/2009.

UKPAR Alphex Pharma (UK) Ltd, Meloxicam 7.5mg and 15mg Orodispersible Tablets
PACKAGE LEAFLET: INFORMATION FOR THE USER
Meloxicam 15 mg Orodispersible Tablets
Meloxicam 15.0 mg

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 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 become 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 orodispersible tablets are and what they are used for
2. Before you take Meloxicam tablets
3. How to take Meloxicam tablets
4. Possible Side Effects
5. Medicine contains aspirin tablets
6. Further Information

1. WHAT MELOXICAM ORODISPERIBLE TABLETS ARE AND WHAT THEY ARE USED FOR
Meloxicam tablets belong to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which can be used to reduce inflammation and pain in joints and muscles. (Orodispersible tablets are tablets which dissolve easily in the mouth.) Meloxicam tablets are used for:
• the short-term treatment of the symptoms of acute attacks of rheumatoid arthritis;
• the long-term treatment of the symptoms of:
  - rheumatoid arthritis;
  - ankylosing spondylitis (a disease of the backbone).

2. BEFORE YOU TAKE MELOXICAM TABLETS
Do not take Meloxicam tablets and tell your doctor if you:
• are allergic to Meloxicam or to any of the other ingredients (See section 4 for a list of these);
• are pregnant, planning to become pregnant or if you are breast-feeding;
• are allergic to aspirin or to other non-steroidal anti-inflammatory medicines (NSAIDs);
• have ever developed signs of asthma (wheezing), nasal polyps along with a runny nose, swelling of the skin or hives rash, when taking aspirin or other anti-inflammatory medicines;
• have or have ever had an ulcer of the stomach or intestines;
• have any kind of bleeding disorder or have ever suffered from bleeding in the stomach or intestines or bleeding in the brain;
• have severe liver disease;
• have severe kidney failure and are not receiving dialysis;
• have end-stage renal failure on haemodialysis;
• suffer from severe heart failure.

If you think any of these apply to you, do not start taking these Meloxicam tablets. Talk to your doctor first and follow the advice given to you.

Take special care with Meloxicam tablets
Tell your doctor or pharmacist before taking this medicine:
• if you have a history of inflammation of the stomach or gut, or any other gastrointestinal disease e.g. ulcerative colitis or Crohn’s disease.
• if you have had high blood pressure;
• if you have heart, liver or kidney disease;
• if you have diabetes;
• if you are elderly (65 years old or more);
• if you have an inherited illness called phenylketonuria, because this medicine contains aspartame (E951);
• if you have been told that you have intolerance to some sugars, because this medicine contains aspartame (E951), a kind of sugar;
• if you have a reduced volume of blood in your body, which may occur if you have serious blood loss or burns, surgery or low fluid intake;
• if you have ever been diagnosed with high potassium levels in the blood;
Tell your doctor if you think any of these apply to you.

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

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

Discuss your treatment with your doctor or pharmacist if you have heart problems, have previously had a stroke or you think you might be at risk of conditions such as high blood pressure, diabetes or high cholesterol or if you are a smoker.

Taking other medicines
When you are taking Meloxicam tablets, do not take any other medicines – including medicines obtained without a prescription – without first talking to your doctor or pharmacist.
• Tell your doctor or pharmacist if you are taking any of the following medicines;
  - any other non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin;
  - medicines to prevent blood clotting, such as warfarin, heparin;
  - medicines to break down blood clots;
  - medicines to treat high blood pressure;
  - oral contraceptives;
  - ciclosporin:
  - any diuretic medicine your doctor may monitor your kidney function if you are taking diuretics;
  - lithium, used to treat mood disorders;
  - selective serotonin reuptake inhibitors, used in the treatment of depression;
  - metformin;
  - citalopram;
  - use of an intrauterine contraceptive device (IUD), usually known as a coil.

Pregnancy and breast-feeding
Meloxicam tablets are not recommended for use by women who are pregnant or breast-feeding.
Tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are breast-feeding.
Ask your doctor or pharmacist for advice before using any medicine.

Children and adolescents (under 16 years old)
This medicine must not be given to children under 16 years old.

Driving and using machinery
Do not drive or operate machinery until you know how Meloxicam tablets affect you. If the tablets make you feel light-headed, dizzy or drowsy, or cause blurred vision, do not drive or operate machinery.

Important information about some of the ingredients of Meloxicam tablets
• These tablets contain the sweetener aspartame (E951), a source of phenylalanine. Contact your doctor before taking them if you have an inherited illness called phenylketonuria.
• These tablets contain sodium (E420), a kind of sugar. If you have ever been told you have intolerance to some sugars, contact your doctor before taking these tablets.

3. HOW TO TAKE MELOXICAM TABLETS
Always take Meloxicam tablets exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure. Read the label carefully.

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Taking this medicine

- Place the tablet in your mouth on your tongue.
- Allow it to dissolve slowly for five minutes (it must never be chewed or swallowed undissolved).
- Swallow with a drink of 240 ml of water.
- If you have a dry mouth, use water to moisten it first.
- Never take more than the recommended maximum dose of 15 mg (one tablet) a day.

Dosage

The dose depends on the medical condition which is being treated. Your doctor will let you know how much you should take.

For the treatment of osteoarthritis:
The usual dose is 7.5 mg (half a tablet) a day. Your doctor may increase your dose to 15 mg (one tablet) a day, if necessary.

For the treatment of rheumatoid arthritis and ankylosing spondylitis:
The usual dose is 15 mg (one tablet) a day. Your doctor may reduce your dose to 7.5 mg (half a tablet) a day if necessary.

If you are aged 65 years and over, the recommended dose for the long term treatment of rheumatoid arthritis and ankylosing spondylitis is 7.5 mg (half a tablet) a day.

If you have any of the conditions listed in Section 2 under the heading 'Take special care with Meloxicam tablets', your doctor may restrict your dose to 7.5 mg (half a tablet) a day.

If you feel that the effect of these Meloxicam tablets is too strong or too weak, or after several days you do not feel any improvement in your condition, consult your doctor or pharmacist.

If you take more of this medicine than you should

Contact your doctor or pharmacist immediately or go immediately to the accident and emergency department of your nearest hospital, taking this leaflet with you.

If you forget to take your tablet (or half tablet)

Never take two doses on the same day to make up for one you have missed.

Take your usual dose the next day.

4. POSSIBLE SIDE EFFECTS

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

- If you have a history of gastrointestinal symptoms while taking anti-inflammatory drugs, your doctor may monitor your progress while you are having this treatment.
- Clinical trials and scientific 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 blood clots in the arteries (which could, for example, lead to heart attack or stroke).

Contact your doctor immediately, or go immediately to the accident and emergency department of your nearest hospital, taking this leaflet or the tablets with you. If you get the following serious side effects:

- severe allergic reactions which may include itching, shortness of breath, skin reactions and asthma attacks (common side effects; affecting less than 1 person in 10);
- bleeding in the stomach or intestines, peptic ulcers, soreness of inflammation of the mouth, or inflammation of the gut (uncommon side effects; affecting less than 1 person in 100);
- severe blanching or peeling of the skin, swelling around the eyes, lips and face, rashes caused by exposure to sunlight (rare side effects; affecting less than 1 person in 1,000).

Contact your doctor if you get the following side effects:

Common side effects (affecting less than 1 person in 10):
- indigestion, feeling or being sick, abdominal pain, constipation, flatulence, diarrhoea, skin rashes or itching;
- light-headedness, headaches;

Uncommon side effects (affecting less than 1 person in 100):
- anaemia;
- nettle rash or hives, pruritus;
- dizziness, drowsiness;
- irregular heart beat, increased blood pressure, hot flushes;
- changes to liver function;
- occult or macroscopic gastrointestinal haemorrhage, stenostatis gastritis;
- salt and water retention, excessive potassium, changes to kidney function, swelling of ankles and legs.

Rare side effects (affecting less than 1 person in 1,000):
- abnormal white blood cell or platelet numbers;
- a hole in the bowel wall, inflammation or soreness of the stomach or intestines ulcers of the stomach or intestine, bleeding and perforations in the stomach or intestines can occur at anytime, rarely in fewer than 1 in every 10,000 patients treated, be fatal;
- palpitations;
- mood swings, tremors, insomnia, nightmares;
- visual disturbances such as blurred vision;
- inflammation of the liver (hepatitis);
- kidney failure.

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 transfer the tablets to another container.
- This product does not require any other special storage requirements in EU countries.
- Do not use Meloxicam 15 mg orodispersible tablets after the expiry date, which is stated on the pack. The expiry date refers to the last day of that month.
- Return all unused medicines to your pharmacist for safe disposal.

6. FURTHER INFORMATION

What Meloxicam 15 mg orodispersible tablets contain

The active ingredient is Meloxicam. Each tablet contains 15 mg.

Other ingredients are mannitol (E421), superfine (E904), croscarmellose sodium (E903), crospovidone (E902), yoghurt flavour, xanthan gum (E415), talc (E903), magnesium stearate (E451), peppermint oil (E933), saccharin sodium (E954), starch (E410), magnesium stearate (E450a), gelatin (E442), talc (E903), sodium lactyl sulphate and magnesium stearate (E572).

What Meloxicam tablets look like and contents of the pack

Meloxicam 15 mg tablets are round, light yellow in color, with a break line which can be divided into equal halves. The tablets are supplied in:
- Boxes containing 3 blister packs of 10 tablets each;
- Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 30 tablets each;
- Boxes with one polyethylene bottle with polypropylene cap with desiccant containing 200 tablets each.

Marketing Authorisation Holder

The Marketing Authorisation Holder in the UK is:
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55
MELOXICAM 15 mg

Orodispersible Tablets

30 Tablets

Method of administration:

Meloxicam 15 mg Orodispersible Tablets should be placed in the mouth on the tongue and allowed to dissolve slowly, for five minutes (the tablet should not be chewed and should not be swallowed followed by a drink of water (e.g. milk).)

For oral administration: Adults and children over 15 years.

To be taken as directed by the prescriber.

Please read enclosed leaflet.

Store in a dry place.

Keep out of the sight and reach of children.

Manufactured by Alpex Pharma SA
Via Cantonale, 5803 Mezzovico (Switzerland)
Distributed by Alpex Pharma (UK) Limited

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