MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.1. Name of the medicinal product:

Melocap 7.5 mg

1.2 (Invented) name of the medicinal product:

Generic Name/INN Name: Meloxicam Tablets BP 7.5 mg

1.3. Strength:

7.5 mg/Tablet

1.3 Pharmaceutical form:

Tablet (Solid oral dosage form)

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specification	Label Claim (mg)	Std. Qty. /Tablet (mg)	%w/w	Function
Material used for Dry Mixing						
1.	Meloxicam*	BP	7.500	7.500	4.832	Active Ingredient
2.	Lactose Monohydrate**	BP	---	81.450	52.481	Diluent
3.	Microcrystalline Cellulose Powder	BP	---	47.500	30.606	Diluent
4.	Potassium Hydroxide Pellets	BP		2.500	1.611	Buffering agent and Dissolution Enhancer
Materials used for binding and paste preparation						
5.	PVPK 30 (Polyvinyl Pyrrolidone K-30)	BP	---	4.000	2.577	Binder
6.	Purified Water ***	BP	---	32.500	---	Coating Solvent
Materials used as Lubricants						
7.	Cros Povidone	BP	---	8.750	5.638	Superdisintegrant
8.	Purified Talc	BP	---	2.500	1.611	Glidant and Lubricant
9.	Magnesium Stearate	BP	---	1.000	0.644	Lubricant
Total wt. of uncoated Tablet				**155.200 mg**	**100%**	

Note: * The quantity of the Meloxicam BP has to be calculated as per the Assay & LOD.

** Quantity of Lactose Monohydrate will vary as per the quantity of the APIs.

*** Used in binding preparation and it is evaporated on drying.

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3. Pharmaceutical form:

Dosage Form: Tablet (Solid oral dosage form)

Visual & Physical characteristics of the product:

A light yellow coloured round shape, flat, uncoated tablets, having a embossed "M" on one side of the tablets.

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:

Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Exacerbations of osteoarthrosis: 7.5mg per day. If necessary, in the absence of improvement, the dose may be increased to 15mg/day. Rheumatoid arthritis, ankylosing spondylitis: 15mg per day (see also “Special populations”). According to the therapeutic response, the dose may be reduced to 7.5mg per day.

Special populations

Elderly patients and patients with increased risks for adverse reactions

The recommended dose for long-term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5mg per day

Renal impairment

In dialysis patients with severe renal failure, the dose should not exceed 7.5mg 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 25ml/min).

Hepatic impairment

No dose reduction is required in patients with mild to moderate hepatic impairment

Paediatric population:

Meloxicam is contraindicated in children and adolescents aged under 16 years

Method of administration

For oral use

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

4.3. Contraindications:

- Hypersensitivity to meloxicam or to any of the excipients or hypersensitivity to substances with a similar action, e.g. NSAID's, aspirin
- Third trimester of pregnancy
- Children and adolescents aged under 16 years
- 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 NSAID's
- Severely impaired liver function
- Non-dialysed severe renal failure
- Gastrointestinal bleeding, history of cerebrovascular bleeding or other bleeding disorders
- 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)
- 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.

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven.

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

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

Meloxicam is not appropriate for the treatment of patients requiring relief from acute pain. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed. Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

Gastrointestinal effects

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

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforations 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

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 the elderly, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin or other nonsteroidal anti-inflammatory drugs, including acetylsalicylic acid given at doses ≥ 500mg as single intake or ≥ 3g as total daily amount.

When gastrointestinal bleeding or ulceration occurs in patients receiving Meloxicam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been

reported in association with NSAID therapy. Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with Meloxicam.

Clinical trial and epidemiological data suggest that use of some NSAIDs including meloxicam (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam. Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of 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. Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with the use of meloxicam.

- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment
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- If the patient has developed SJS or TEN with the use of meloxicam, meloxicam must not be restarted in this patient at any time.

Parameters of liver and renal function

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen and other laboratory disturbances, have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of Meloxicam should be stopped and appropriate investigations undertaken.

Functional renal failure

NSAIDs, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependent. 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
- Hypovolaemia (whatever the cause)
- Congestive heart failure
- Renal failure
- Renal failure
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin < 25g/l or Child-Pugh score > 10)

In rare instances, 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 7.5mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25ml/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. 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.

Hyperkalaemia

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase kalaemia. Regular monitoring of potassium values should be performed in such cases.

Combination with pemetrexed

In patients with mild to moderate renal insufficiency receiving pemetrexed, meloxicam should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Other warnings and precautions

Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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

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

Meloxicam contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 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.

Risks related to hyperkalaemia

Certain medicinal products or therapeutic groups may promote hyperkalaemia:

potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs, (low-

molecular-weight or unfractionated) heparins, ciclosporin, tacrolimus and trimethoprim. The onset of hyperkalaemia may depend on whether there are associated factors.

This risk is increased when the above-mentioned medicinal products are co-administered with meloxicam.

Pharmacodynamic Interactions

Other non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid

Combination (see section 4.4) with other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at doses ≥500mg as single intake or ≥ 3g as total daily amount is not recommended. Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect.

Corticosteroids (e.g. Glucocorticoids):

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

Anticoagulant or heparin

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

NSAIDs may enhance the effects of anti-coagulants, such as warfarin. The concomitant use of NSAIDs and anticoagulants or heparin administered in geriatrics or at curative dose is not recommended.

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

Thrombolytics and antiplatelet 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.

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.

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. ciclosporin, tacrolimus) Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

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.

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

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

Pharmacokinetic Interactions: Effect of other drugs on the pharmacokinetics of meloxicam

Cholestyramine

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

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

4.6. Pregnancy and lactation:

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, meloxicam should not be given unless clearly necessary. If meloxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose:

The foetus to

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis the month and the neonate at the end of pregnancy to
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis the month and the neonate at the end of pregnancy to
- Inhibition of uterine contractions resulting in delayed or prolonged labour
- Consequently, Meloxicam is contraindicated during the third trimester of pregnancy

Breast-feeding

While no specific experience exists for meloxicam, NSAIDs are known to pass into mother's milk. Administration therefore is not recommended in women who are breastfeeding.

Fertility

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

4.7. Effects on ability to drive and use machines:

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

4.8. Undesirable effects:

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events

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

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

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in 27 clinical trials with a treatment duration of at least 14 days. The information is based on clinical trials involving 15197 patients who have been treated with daily oral doses of 7.5 or 15mg meloxicam tablets or capsules over a period of up to one year. Adverse drug reactions that have come to light as a result of reports received in relation to administration of the marketed product are included.

The frequency grouping is defined using the following convention:

Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table A: Adverse reactions possibly or probably related to meloxicam based on clinical trial experience and post-marketing surveillance:

Blood and lymphatic system disorders: Anaemia, Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia.

Immune system disorders: Hypersensitivity, allergic reactions other than anaphylactic or anaphylactoid reactions, anaphylactic reaction, anaphylactoid reaction

Psychiatric disorders: Mood altered, nightmares, Confusional state, disorientation

Nervous system disorders: Headache, Dizziness, somnolence

Eye disorders: Visual disturbance including vision blurred; conjunctivitis

Ear and labyrinth disorders: Vertigo, Tinnitus

Cardiac disorders: Palpitations

Vascular disorders: Blood pressure increased, flushing

Respiratory, thoracic and mediastinal disorders: Asthma in individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhea, Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation, Colitis, gastroduodenal ulcer, oesophagitis, Gastrointestinal perforation

Hepatobiliary disorders: Liver function disorder (e.g. raised transaminases or bilirubin), Hepatitis

Skin and subcutaneous tissue disorders: Angioedema, pruritus, rash, Stevens-Johnson syndrome, toxic, epidermal necrolysis, urticarial, Dermatitis bullous, erythema multiforme

Renal and urinary disorders: Sodium and water retention, hyperkalaemia, renal function test abnormal (increased serum creatinine and/or serum urea), Acute renal failure in particular in patients with risk factors.

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

4.9. Overdose:

Symptoms

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment

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

5. Pharmacological properties:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Non-Steroidal Anti-Inflammatory agent, Oxicams,

ATC code: M01A C06

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.

Mechanism of action

The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAIDs (including Meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

5.2. Pharmacokinetic properties:

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent. Following single dose administration of meloxicam, median maximum plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets). With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to mean drug plasma concentrations with a relatively small peaktrough fluctuation in the range of 0.4 - 1.0µg/mL for 7.5mg doses and 0.8 - 2.0µg/mL for 15mg doses, respectively (Cmin and Cmax at steady state, correspondingly). Mean maximum plasma concentrations of meloxicam at steady state are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

Distribution

Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, i.e. approx. 11L after i.m. or i.v. administration, and shows interindividual variation in the order of 30-40%.

Biotransformation

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

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 of 7.5mL/min.

Linearity/non-linearity

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

Special Populations

Hepatic and Renal impairment Neither hepatic, nor mild to moderate renal insufficiency has a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significant higher total drug clearance. A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5mg must not be exceeded.

Elderly

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

5.3 Preclinical safety data

The toxicological profile of meloxicam has been found in preclinical studies to be identical to that of NSAIDs: gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species. Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects

(increase of resorptions) at maternotoxic dose levels at 1mg/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 80mg/kg in rabbits. The affected dose levels exceeded the clinical dose (7.5-15mg) by a factor of 10 to 5- fold on a mg/kg dose basis (75kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. No evidence has been found of any mutagenic effect, either in vitro or in vivo. No carcinogenic risk has been found in the rat and mouse at doses far higher than those used clinically.

6. Pharmaceutical particulars:

6.1. List of Excipients:

Tablet core:

- Lactose Monohydrate
- Microcrystalline Cellulose Powder
- Potassium Hydroxide Pellets
- PVPK 30 (Polyvinyl Pyrrolidone K-30)
- Purified Water
- Crospovidone
- Purified Talc
- Magnesium Stearate

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life: 36 months

6.4. Special precautions for storage:

Store at a temperature not exceeding 30°C.

6.5. Nature and contents of container:

Primary packing: 10 tablets in ALU-PVC Blister Pack

Secondary packing: Such a 01 Blister are packed in Printed Monocarton along with Package Insert.

6.6. Special precautions for disposal:

No special requirements.

MODULE 1 – ADMINISTRATIVE PARTICULARS OF THE PRODUCT

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

7. Registrant:

Evans Therapeutics Limited.

No. 24, Abimbola Way, Isolo Industrial Estate, Isolo. Lagos, Nigeria

E-mail: olanihun.temitope@evanstherapeutics.com