IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0372/010/001
Case No: 2035984

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Sandoz Ltd

37 Woolmer Way, **Bordon**, **Hants GU35 9QE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Meloxicam 7.5mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **16/10/2007** until **06/09/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Meloxicam 7.5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains meloxicam 7.5 mg.

Excipients: 43 mg lactose monohydrate/tablet.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Meloxicam Sandoz, 7.5 mg tablets: Pale yellow coloured round tablet with a score line on one side .

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term symptomatic treatment of 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.
If necessary, in the absence of improvement, the dose may be increased to 15 mg/day.

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

According to the therapeutic response, the dose may be reduced to 7.5 mg/day.

DO NOT EXCEED THE DOSE OF 15 mg/day.

As the risks associated with the use of meloxicam may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

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

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:
Meloxicam should not be used in children aged under 15 years.

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

4.3 Contraindications

This medicinal product is contra-indicated in the following situations :
- pregnancy and lactation (See section 4.6)
- hypersensitivity to meloxicam or to any of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs (Non-Steroidal anti-inflammatory drugs), Acetyl salicylic acid. Meloxicam Sandoz should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic edema or urticaria following the administration of aspirin or other NSAIDs (Non-Steroidal anti-inflammatory drugs).
- active gastro-intestinal ulcer or history of recurrent gastro-intestinal ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- severely impaired liver function;
- non-dialysed severe renal failure;
- gastrointestinal bleeding or perforation, related to previous NSAIDs therapy, 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).

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

- Patients with gastrointestinal symptoms or history of gastrointestinal disease (i.e. ulcerative colitis, Crohn's disease) should be monitored for digestive disturbances, especially for gastrointestinal bleeding as their condition may be exacerbated (see section 4.8).

- Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
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- As with other NSAIDs (Non-Steroidal anti-inflammatory drugs), gastrointestinal bleeding or ulceration/perforation, in rare cases fatal, have been reported with meloxicam at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The risk of gastrointestinal bleeding is higher with increased NSAID (Non-Steroidal anti-inflammatory drugs) doses, in patients with a history

of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3). Gastrointestinal bleeding or ulceration/perforation have in general more serious consequences in the elderly (see section 4.8). 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see section 4.5).

- **If gastrointestinal bleeding or ulceration occurs in patients receiving Meloxicam, the drug should be withdrawn. Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stage of treatment.**

- The possible occurrence of severe skin reactions and serious life threatening hypersensitivity reactions (i.e. anaphylactic reactions) is known to occur with NSAIDs including oxicams. The highest risk for these reactions exists early in the course of therapy, the onset of the reaction occuring mainly within the first month of treatment. In those cases, Meloxicam should be withdrawn immediately and careful observation is necessary.

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

- As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin 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.

- Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics and consequently possible exacerbations of the condition of patients with cardiac failure or hypertension may occur with NSAIDs (see sections 4.2 and 4.3).

- 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, (such as sartans), diuretics (see section 4.5.)
  - hypovolaemia (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)'

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

- 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 recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.**

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

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

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

- Caution is required if meloxicam is administered to patients suffering from, or with a previous history of, bronchial asthma since there is a possibility that NSAIDs could cause bronchospasm in such patients.

- Meloxicam should not be used in children aged under 15 years

- ***Cardiovascular and cerebrovascular effects***:
  Appropriate monitoring and advice are required for patients with a history of hyertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

  Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Meloxicam.

  Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

This medicinal product contains lactose.

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

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic Interactions:

Other NSAIDs, including salicylates (acetylsalicylic acid ≥ 3g/d):
Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended (see section 4.4).

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Oral anticoagulants:
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. The concomitant use of NSAIDs and oral anticoagulants is not recommended . NSAIDs may enhance the effects of anti-

coagulants, such as warfarin (see section 4.4).
Careful monitoring of the INR is required if it proves impossible to avoid such combination.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (See section section 4.4)

Diuretics, ACE inhibitors and Angiotensin-II Antagonists (such as sartans):
NSAIDs (including acetylsalicylic acid at doses ≥ 3 g/d) 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-administratin 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.

Cyclosporin:
Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

Intrauterine devices:
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 hematological toxicity of methotrexate can be amplified by treatment with NSAID drugs (see above). (See section 4.8)

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

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

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

4.6 Pregnancy and lactation

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

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, meloxicam is contraindicated during pregnancy (see section 4.3).

Lactation
While no specific experience exists for meloxicam, NSAIDs (Non-Steroidal anti-inflammatory drugs) are known to pass into mother’s milk. The use of meloxicam is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

Meloxicam has no or negligible influence on the abilitiy to drive and use machines. However, when visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

4.8 Undesirable effects

a) General Description
The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in clinical trials. The information is based on clinical trials involving 3750 patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).
Adverse drug 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 (≥ 1/1.000, < 1/100); rare (≥ 1/10.000, < 1/1.000); very rare (< 1/10.000)

b) Table of adverse reactions

Blood and the lymphatic system disorders
Common : Anemia

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

Immune system disorders
Rare : Anaphylactic / anaphylactoid reactions

Psychiatric disorders
Rare : Mood disorders, insomnia and nightmares

Nervous system disorders
Common : Light-headedness, headache

Uncommon : Vertigo, tinnitus, drowsiness

Rare : Confusion

Eye disorders
Rare : Visual disturbances including blurred vision

Cardiac disorders
Uncommon : Palpitations

Frequency not known: Cardiac failure

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

Respiratory, thoracic and mediastinal disorders
Rare : Onset of asthma attacks in certain individuals allergic to acetyl salicylic acid or other NSAIDs

Gastrointestinal disorders
Common : Dyspepsia, nausea and vomiting symptoms, hematemesis, abdominal pain, constipation, flatulence, diarrhea, melaena

Uncommon : Gastrointestinal bleeding, gastroduodenal ulcers, esophagitis, ulcerative stomatitis

Rare : Gastrointestinal perforation, gastritis, colitis

The peptic ulcers, perforation or gastrointestinal bleeding, that may occur can be sometimes fatal, especially in elderly (see section 4.4). Exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration.

Hepato-biliary disorders
Rare : Hepatitis

Skin and subcutaneous tissue disorders
Common : Pruritus, rash

Uncommon : Urticaria

Rare : Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions

Very rare : bullous reactions such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, exfoliative dermatitis

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

General disorders and administration site conditions
Common : Edema including edema of the lower limbs.

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

Uncommon : Disturbance of laboratory tests investigating renal function (e.g. raised creatinine or urea)

c) Information Characterising Individual Serious and/or Frequently Occurring Adverse Reactions
Isolated cases of agranulocytosis have been reported in patients treated with meloxicam and other potentially myelotoxic drugs (see section 4.5).

d) ***Adverse reactions which have not been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class***
Organic renal injury probably resulting in acute renal failure: isolated cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome, and papillary necrosis have been reported. (see section 4.4)

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

4.9 Overdose

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.
Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Inflammatory and antirrheumatic products, non-steroids; Oxicams
ATC Code: M01AC06

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

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

5.2 Pharmacokinetic properties

Absorption
Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent.
Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).
With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

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

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

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

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

Special populations

Hepatic/renal Insufficiency:
Neither hepatic, mild nor moderate renal insufficiency have a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded (see section 4.2, 4.3).

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 80 mg/kg in rabbits.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters of PVC/PVdC and hard tempered Aluminium foil. Cartons of 7, 10, 14, 15, 20, 28, 30, 50, 60, 100, 140, 280, 300, 500, or 1000 tablets, (not all pack sizes may be marketed).

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd.
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Bordon
Hants
GU35 9QE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 372/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th September 2007

10 DATE OF REVISION OF THE TEXT

October 2007