SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melox 10 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Meloxicam 10mg/ml.
One ml of solution contains 10 mg of meloxicam.
One ampoule with 1.5 ml solution for injection contains 15 mg of meloxicam.

Excipient with known effect: Sodium.
Each ml of solution contains 1.29 to 1.41 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, yellow to greenish-yellow solution, practically free from particles.
The pH of the solution is 8.4 – 8.9

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of acute exacerbations of rheumatoid arthritis and ankylosing spondylitis, where the oral and rectal route may not be used.
Melox is indicated in adults.

4.2 Posology and method of administration

Posology
1 ampoule of 15 mg once a day, administered intramusculary.
DO NOT EXCEED THE DOSE OF 15 mg/day.
Treatment will normally be limited to a single injection for treatment initiation, with a maximum duration of administration of 2 to 3 days in exceptional cases (for example, when the oral and rectal route may not be used).

Undesirable effects may be minimized 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.

Special populations

Elderly patients and patients at increased risk of adverse effects (see section 5.2)

In the elderly, the recommended dose is 7.5 mg / day. In patients with an increased risk of side effects, treatment should begin at a dose of 7.5 mg daily (1 / 2 ampoule of 15mg) (see section 4.4).

Renal impairment (see section 5.2)

In patients with renal impairment undergoing hemodialysis, dosage should not exceed 7.5 mg / day (1/2 ampoule of 15mg). No dosage reduction is necessary in patients with mild to moderate renal impairment (ie patients with a creatinine clearance over 25 ml / min). For patients with severe renal failure not dialyzed, see section 4.3.

Hepatic impairment (see section 5.2)

No dose reduction is necessary in patients with mild to moderate hepatic impairment. For patients with severe hepatic impairment, see section 4.3.

Paediatric population

Melox 10 mg / ml solution for injection is contraindicated in children and adolescents aged under 18 years (see section 4.3).

Method of administration

For intramuscular injection.

Injections should be made in a strictly aseptic manner in the outer part of the upper outer quadrant of the buttock, deeply and slowly. When repeated, it is recommended to switch sides with each injection.

It is important to aspirate before injecting to ensure that the needle tip is not in a vessel.

In case of severe pain at the time of injection, stop it immediately.

In case of hip replacement, the injection must be made on the opposite side.

4.3 Contraindications

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

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- third trimester of pregnancy (see section 4.6);
- children and adolescents aged under 18 years;

- hypersensitivity to the active molecules with a similar action, e.g. NSAIDs, acetylsalicylic acid. Melox should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic edema or urticaria following the administration of acetylsalicylic acid 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);
- gastrointestinal bleeding, history of cerebral hemorrhage or other bleeding disorders;
- severely impaired liver function;
- non-dialysed severe renal failure;
- severe heart failure.
- coagulation disorders or anticoagulant therapy in progress (contraindications related to the intramuscular route).

4.4 Special warnings and precautions for use

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

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. The use of meloxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Melox 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 history of these disorders.

Gastrointestinal effects

Gastrointestinal bleedings, ulcerations or perforations, which can be fatal, have been reported with all NSAIDs at anytime 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 perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose

available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastro intestinal 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 ($\geq$ 1g as single dose intake or $\geq$ 3g as total daily amount) (see section 4.5).

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 (see section 4.8).

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

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.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, meloxicam treatment should be discontinued.
The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
If the patient has developed SJS or TEN with the use of meloxicam, meloxicam must not be re-started in this patient at any time.

Cases of fixed drug eruption (FDE) have been reported with meloxicam. Meloxicam should not be reintroduced in patients with history of meloxicam-related FDE. Potential cross reactivity might occur with other oxicams.

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 Melox 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 $\geq$ 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. in 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.

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 (see section 4.2).

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

As with all NSAIDs administered by intramuscular route, abscesses and necrosis may occur at the injection site. 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.

Melox contains -sodium

This medicine contains less than 1 mmol sodium (23 mg) per, ampoule,. That is to say essentially ‘sodium- free’.

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/day:

The concomitant administration (see section 4.4) with other non steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g per dose or ≥ 3g per day) is not recommended (see section 4.4).

Corticosteroids (e.g. Glucocorticoids):
The concomitant use with corticosteroids requests caution because of an increased risk of bleeding or gastrointestinal ulceration.

Anticoagulants and heparin administered in geriatrics or at curative doses:
Significantly increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). The concomitant use of NSAIDs and anticoagulants or heparin administered in the elderly 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 the association cannot be avoided.

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 receptor antagonists of angiotensin II treatments 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 agents (including beta-blockers):
As with inhibitors of angiotensin converting enzyme and antagonists of angiotensin II, 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 calcineurin inhibitors may be enhanced by NSAIDs via renal prostaglandin mediated effects. When used in combination, renal function should be monitored, 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 due to 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 association appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, with 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. When used in combination, monitoring of blood cell counts and renal function are needed. Special precautions are required in case of simultaneous administration of methotrexate and NSAIDs on 3 consecutive days, because of the risk of toxicity associated with increased plasma levels of methotrexate.

Although the pharmacokinetics of methotrexate (15mg/week) was not significantly altered by concomitant administration of meloxicam, 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 This effect causes an increase in the clearance of meloxicam by 50% and the half-life decreases to 13+3 hrs.

This interaction has a clinical significance.

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

4.6 Fertility, 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 is increased by less than 1%, to about 1.5 %. The risk is assumed to increase with dose and duration of threatment.

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 observed in animals treated with a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, meloxicam use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to meloxicam for several days from gestational week 20 onward. Meloxicam should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension).
- impaired renal function (see above);

- 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 (see section 4.3 and 5.3).

Breast-feeding

Meloxicam passes into breast milk. The benefit of the treatment to the mother and the benefit of breast feeding to the child must be weighed against the possible adverse effects on the suckling child.

Fertility

If meloxicam is used by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible.

4.7 Effects on ability to drive and use machines

No specific studies on the ability to drive and use machines have been performed. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, is it is unlikely that meloxicam affects the ability to drive or operate machinery. However, when visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is recommended to refrain from driving and operating machinery.

4.8 Undesirable effects

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 gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis has been observed.

The frequencies of adverse drug reactions given below are based on corresponding occurrences of reported adverse events in 27 clinical trials with treatment duration of at least 14 days. The

information is based on clinical trials involving 15197 patients treated with daily oral doses of 7.5 or 15 mg 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.

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

- very common (≥1/10);
- common (≥1/100 to <1/10);
- uncommon (≥1/1,000 to <1/100);
- rare (≥1/10,000 to <1/1,000);
- very rare (<1/10,000),
- not known (cannot be estimated from the available data).

Table of adverse reactions

Blood and lymphatic system disorders

Uncommon: Anaemia

Rare: Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia

Very rare cases of agranulocytosis have been reported.

Immune system disorders

Uncommon: Allergic reactions other than anaphylactic or anaphylactoid reactions

Not known: Anaphylactic shock, anaphylactic /anaphylactoid reactions

Psychiatric disorders

Rare: Mood altered, nightmares

Not known: Confusional state, disorientation

Nervous system disorders

Common: Headache

Uncommon: Dizziness, somnolence

Eye disorders

Rare: Visual disturbance including blurred vision; conjunctivitis

Ear and labyrinth disorders

Uncommon: Vertigo

Rare: Tinnitus

Cardiac disorders

Rare: Palpitations

Cardiac failure has been reported in association with NSAID treatment.

Vascular disorders

Uncommon: Blood pressure increased (see section 4.4), flushing

Respiratory, thoracic and mediastinal disorders

Rare: Asthma in individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders

Very common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea

Uncommon: Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation

Rare: Colitis, gastroduodenal ulcer, oesophagitis

Very rare: Gastrointestinal perforation

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

Not known: Pancreatitis.

Hepatobiliary disorders

Uncommon: Liver function disorder (e.g. raised transaminases or bilirubin)

Very rare: Hepatitis

Skin and subcutaneous tissue disorders

Uncommon: Angioedema, pruritus, rash

Rare: urticaria

Very rare: Dermatitis bullous, erythema multiforme; Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

Not known: Photosensitivity reaction, fixed drug eruption (see Section 4.4).

Renal and urinary disorders

Uncommon: Sodium and water retention, hyperkalaemia (see section 4.4. and section 4.5.), renal function test abnormal (increased serum creatinine and/or serum urea)

Very rare: Acute renal failure in particular in patients with risk factors (see section 4.4.)

General disorders and administration site conditions

Common: injection site mass, pain at the injection site.
Uncommon: Oedema including oedema of the lower limbs.

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).

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
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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system [To be completed nationally]

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 during treatment with NSAIDs and may occur in overdose.
Patients should be managed with symptomatic and supportive care following an NSAID overdose.
In a clinical trial, an acceleration of the elimination of meloxicam has been demonstrated following the oral administration of cholestyramine (4 g, 3 times daily).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Inflammatory and Antirheumatic Products, Non Steroids, Oxicams
ATC code: M01AC06

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

5.2 Pharmacokinetic properties

Absorption

Meloxicam is completely absorbed after intramuscular injection. In comparison, the bioavailability of meloxicam following oral administration is on average 89%. No dose adjustments are necessary when switching from injectable to oral administration. After intramuscular injection of a dose of 15 mg, peak plasma concentration is about 1.62 mg / l, and it is reached in about 60 minutes.

Distribution

Meloxicam is strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid where it gives 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 is intensely metabolised in the liver. Four different metabolites, all pharmacologically inactive, have been identified in the urine. The major metabolite, 5'-carboxymeloxicam (corresponding to 60% of the dose) is formed by oxidation of an intermediate metabolite, 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (corresponding to 9% of the dose). In vitro studies suggest that CYP2C9 plays an important role in this metabolic pathway with a minor contribution of CYP3A4. The peroxidase activity is probably the source of two other metabolites, which correspond respectively to 16 and 4% of the administered dose.

Elimination

Meloxicam is eliminated primarily as metabolites, in urine, half and half in the faeces. Less than 5% of the daily dose is excreted unchanged in the faeces, only traces of meloxicam were left unchanged in the urine.
The mean half-life of elimination is approximately 20 hours. Total plasma clearance was 8 ml / min on average.

Linearity/non-linearity:

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

Special populations

Hepatic/renal Insufficiency: Neither hepatic, nor mild to moderate renal insufficiencies have a substantial effect on meloxicam pharmacokinetics. In case of severe renal failure, the increase in the volume of distribution may result in higher unbound meloxicam concentrations. The daily dose of 7.5mg should not be exceeded in this case (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

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meglumine,
Glycofurol,
Poloxamer 188,
Sodium chloride,
Glycine,
Sodium hydroxide (for pH adjustment),
Butylhydroxytoluene,
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Clear glass ampoule with total fill capacity of 2 ml, containing 1,5 ml solution for injection.
The ampoules are packed in blisters, 5 ampoules in one moulded PVC blisters sealed by a PE foil.
Boxes with 5 ampoules. Each box contains 1 blister with 5 ampoules.
Boxes with 10 ampoules. Each box contains 2 blisters with 5 ampoules.
Boxes with 100 ampoules. Each box contains 20 blisters with 5 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Only clear solution without particles should be used.
The solution is for single use. Any unused solution should be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 January 2014

10. DATE OF REVISION OF THE TEXT

25-AUG-2023