DISPERSIBLE PIROXEN

Piroxicam

Summary of product characteristics

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1. NAME OF THE MEDICINAL PRODUCT

DISPERSIBLE PIROXEN 20 mg, dispersible tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For a dispersible tablet

Principe actif active ingredient :
PIROXICAM …… 20mg
Excipients :
Carboxymethyl starch Sodium …….. 12.5mg
Cellulose, Microcristalline …… 461.50 mg
Silice colloidale anhydre …… 3.00mg
Stearate de Magnesium ……. 3.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

4. CLINICAL DATA

4.1. Therapeutic indications

They are limited in adults and children older than 15 years:

1 / long-term symptomatic treatment of:

- Chronic inflammatory rheumatism, including rheumatoid polyarthritis, ankylosing spondylitis (or related syndromes such as Fiessinger-Leroy-Reiter syndrome and psoriatic rheumatism);

- certain painful and disabling arthroses;

2 / short-term symptomatic treatment of acute onset of:

- Abarticular rheumatism such as scapulohumeral periarthritis, bursitis tendinitis

- acute post-traumatic conditions of the musculoskeletal system

- microcrystalline arthritis

- arthrosis

- radiculalgia.

- treatment of primary dysmenorrhoea.

4.2. Dosage and method of administration

Administration method
Oral way.
The tablet can be swallowed or dissolved in a large glass of water.

Dosage

Prescribing specialties containing piroxicam should be initiated by physicians experienced in the diagnosis and treatment of patients with inflammatory or degenerative rheumatic diseases.
The maximum recommended daily dose is 20 mg.
The occurrence of adverse effects may be minimized by using the lowest necessary symptom relief dose for the shortest course of treatment. The benefit and safety of the treatment should be re-evaluated within 14 days.
If further treatment is needed, it should be accompanied by frequent reassessments.
Because piroxicam has been associated with an increased risk of gastrointestinal complications, the use of a protective therapy of the gastric mucosa (eg, misoprostol or proton pump inhibitors) needs to be seriously considered. , especially for elderly patients.

Frequency of administration

The tablet should be taken during a meal.

CYP2C9 slow metabolizers

As the risk of dose-related adverse events is higher, piroxicam should be given with caution to patients known or suspected to be poor CYP2C9 metabolizers, based on genotyping or previous antecedents / experiences with other substrates of CYP2C9. A reduction of the dose should be considered (see section 5.2).

4.3. Contraindications

This medicine is contraindicated in the following situations:

· Beyond 24 weeks of amenorrhea (5 months of pregnancy completed),

· Hypersensitivity to the active substance, history of skin reaction (irrespective of severity) to piroxicam, other NSAIDs and other drugs,

· History of allergy to other components of the capsule,

· History of asthma triggered by taking piroxicam or other substances of similar activity such as other NSAIDs, aspirin,

· A history of serious allergic drug reactions of any type, particularly skin reactions such as polymorphic erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome),

· Concomitant use of other NSAIDs, including COX-2 selective NSAIDs and acetylsalicylic acid, at analgesic doses,

· Concomitant use of anticoagulants,

· History of ulcer, haemorrhage or gastrointestinal perforation,

· Patients with a history of gastrointestinal disorders predisposing patients to bleeding disorders such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis,

· Patients with active peptic ulcer, inflammatory gastrointestinal disorder or gastrointestinal hemorrhage,

· Severe hepatocellular insufficiency,

· Severe heart failure,

· Severe renal insufficiency,

· Children under 15 years old.

4.4. Special warnings and precautions for use

❖ **Special warnings**

The occurrence of adverse effects may be minimized by using the lowest possible dose for the shortest duration of treatment required for symptomatic relief and the paragraphs "Gastrointestinal events" and "Cardiovascular and cerebrovascular effects" below).

Clinical benefit and security of use should be periodically re-evaluated. Treatment should be stopped immediately at the first sign of skin reactions or symptomatic gastrointestinal events.

Patients with asthma associated with chronic rhinitis, chronic sinusitis and / or nasal polyposis have a higher risk of allergic manifestation when taking aspirin and / or nonsteroidal anti-inflammatory drugs than the rest of the population.

The administration of this drug may lead to an asthma attack, especially in some people allergic to aspirin or NSAID.

Gastrointestinal (GI) manifestations: risk of GI ulcers, hemorrhages and perforations

NSAIDs, including piroxicam, can cause serious gastrointestinal adverse events, including hemorrhages, ulcerations, and perforations of the stomach, small intestine, or large intestine,

some of which may be fatal. These serious adverse events can occur at any time, without warning signs, in all patients treated with NSAIDs.

Whether short-term or long-term, NSAID treatment increases the risk of serious GI side effects. Studies have suggested that piroxicam may be associated with a higher risk of serious gastrointestinal toxicity compared to other NSAIDs.

Patients with risk factors for serious GI adverse reactions should be treated with piroxicam only after careful evaluation of the benefit / risk ratio (below). The possibility of protective treatment of the gastric mucosa (eg misoprostol or proton pump inhibitors) should be seriously considered.

Serious GI complications

Identification of subjects at risk

The incidence of serious GI complications increases with age. Beyond age 70, there is a high risk of complications. Administration in patients older than 80 years should be avoided.

Patients receiving combination therapies, such as oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or platelet aggregation inhibitors such as low-dose acetylsalicylic acid, are at increased risk of serious GI complications. (See below. As with other NSAIDs, the use of piroxicam in combination with gastric mucosal protective therapy (eg, misoprostol or proton pump inhibitors) should be considered for these at-risk patients.

Patients and physicians should be vigilant to detect any signs and symptoms of ulcer and / or gastrointestinal bleeding during piroxicam therapy. Patients should be asked to report any new or unusual abdominal symptoms during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately. Further clinical evaluation and a therapeutic alternative should be considered.

Cardiovascular and cerebrovascular effects

Adequate monitoring and recommendations are required in patients with a history of hypertension and / or mild to moderate heart failure, with reports of water-sodium retention and edema associated with NSAID therapy.

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (especially when used at high doses and over a long period of time) may be associated with a small increase in the risk of arterial thrombotic events (eg, infarction myocardium or cerebrovascular accident). There is currently insufficient data to rule out this risk increase for piroxicam.

Patients with uncontrolled hypertension, congestive heart failure, ischemic heart disease, peripheral arterial disease, and / or with a history of stroke (including transient ischemic attack) should be treated with piroxicam only. after a careful evaluation of the benefit / risk ratio.

Similar attention should be paid before initiating any long-term treatment in patients with risk factors for cardiovascular disease (such as hypertension, hyperlipidemia, diabetes or smoking).

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been very rarely reported during treatment with NSAIDs. Studies have suggested that piroxicam may be associated with a higher risk of serious skin reactions than other NSAIDs not derived from oxicams. The

incidence of these adverse effects appears to be greater at the beginning of treatment and in the majority of cases, they appear during the first month of treatment. Treatment with piroxicam should be discontinued at the onset of rash, mucosal lesions, or other signs of hypersensitivity.

Functional renal insufficiency

By inhibiting the vasodilator action of renal prostaglandins, NSAIDs are likely to cause functional renal failure by decreasing glomerular filtration.

At the start of treatment, monitoring of diuresis and renal function is recommended for patients with the following risk factors:

· Elderly subjects,

· Associated drugs such as: CEI, sartans, diuretics.

· Hypovolemia, whatever the cause,

· heart failure,

· Chronic renal failure,

· nephrotic syndrome,

· Lupus nephropathy,

· Decompensated hepatic cirrhosis.

Water-Sodium Retention

Water-Sodium retention with possibility of edema, hypertension or increase of hypertension , aggravation of heart failure. Clinical monitoring is required at the beginning of treatment in case of hypertension or heart failure. A decrease in the effect of antihypertensives is possible

Hyperkaliémie

In case of hyperkalemia favored by diabetes or treatment with potassium-sparing drugs, Regular monitoring of serum potassium should be performed.

Medical prescriptions should take into account the fact that infertility by non-rupture of the De Graaf follicle and reversible at the end of treatment, have been described in long-term treated patients with certain inhibitors of prostaglandins synthesis.

Due to the presence of lactose, this drug is contraindicated in cases of congenital galactosemia, glucose-galactose malabsorption syndrome or lactase deficiency.

❖ **Precautions for use**

This medicine exists in other dosages that may be more suitable.

The onset of asthma attack in some subjects may be related to an allergy to aspirin or NSAIDs.

Special attention should be given to patients with a history of hypertension and / or heart failure, with cases of water and sodium retention and edema that had been reported in combination with NSAID therapy.

Patients known to be poor metabolisers of CYP2C9 should be treated with caution.

4.5. Interactions with other drugs and other forms of interactions

Risk related to hyperkalemia

Certain drugs or therapeutic classes may promote the occurrence of hyperkalemia: potassium salts, potassium-sparing diuretics, converting enzyme inhibitors, angiotensin II inhibitors, nonsteroidal anti-inflammatory drugs, heparins (low molecular weight or unfractionated), ciclosporin and tacrolimus, trimethoprim.
The occurrence of hyperkalemia may depend on the existence of co-associated factors.
This risk is increased in case of combination of the above-mentioned drugs.
The simultaneous administration of piroxicam with the following products requires a rigorous monitoring of the clinical and biological status of the patient.

Contraindicated combinations

+ Other NSAIDs (including aspirin and other salicylates)

As with all NSAIDs, the combination of piroxicam with acetylsalicylic acid or other NSAIDs, as well as the combination of several specialties containing piroxicam should be avoided.
No data has shown the benefit of such combinations compared with piroxicam used alone; in addition, the incidence of adverse effects is increased. Studies in humans have shown a reduction in the plasma concentration of piroxicam by approximately 80% of the usual value in the case of concomitant administration of piroxicam and acetylsalicylic acid.
+ Anticoagulants
NSAIDs, including piroxicam, may augment the effects of anticoagulants, such as warfarin. Therefore, concomitant use of piroxicam and anticoagulants such as warfarin should be avoided.

Not recommended combinations

+ Unfractionated heparins, low molecular weight heparins and related (in curative doses or in the elderly)
Increased risk of haemorrhage (inhibition of platelet function and aggression of gastric and duodenal mucosa by NSAIDs).
If the association can not be avoided, close clinical supervision is necessary. Do not exceed a few days of treatment with NSAIDs.
+ Lithium
Increased lithemia that can reach toxic values (decreased renal excretion of lithium).
If the combination can not be avoided, closely monitor lithium and adjust its dosage during the combination and after stopping the NSAID.
+ Methotrexate used at doses greater than 15 mg / week
Increased hematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory drugs).
+ Pemetrexed (patients with mild to moderate renal function, creatinine clearance between 45 ml / min and 80 ml / min)
Risk of increased toxicity of pemetrexed (decreased renal clearance by NSAIDs).

combination warnings

+ Diuretics, Enzyme Inhibitors (ACE), Angiotensin II Inhibitors
Acute renal failure in the patient at risk (elderly and / or dehydrated) by reduction of glomerular filtration (inhibition of vasodilator prostaglandins by NSAIDs).
Hydrate the patient. Monitor the kidney function at the start of the treatment.
+ Methotrexate used at doses less than 15 mg / week
Increased toxicity; particularly hematological of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory drugs).
Weekly control of the complete blood count during the first weeks of the association. Increased monitoring for (even mildly) impaired renal function, as well as in the elderly.

+ Pemetrexed (patients with normal kidney function)
Risk of increased toxicity of pemetrexed (decreased renal clearance by NSAIDs).
Biological monitoring of the renal function.

combinations to consider

+ Acetylsalicylic acid at anti-aggregating doses (from 50 mg to 375 mg daily in 1 or more doses)
increase in ulcerogenic and digestive hemorrhage risk
+ Glucocorticosteroids administered orally (except hydrocortisone as a replacement therapy)
Increased risk of ulceration and gastrointestinal haemorrhage
+ Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)
Increased risk of gastrointestinal haemorrhage
+ Unfractionated Heparins, Low Molecular Weight Heparins (Preventive Doses)
Increased haemorrhagic risk
+ Beta-blockers (except esmolol)

Reduction of antihypertensive effect (inhibition of vasodilator prostaglandins by NSAIDs and retention of water and sodium with NSAIDs pyrazole).

+ Ciclosporin, tacrolimus

Risk of addition of nephrotoxic effects, especially in the elderly.
Monitor renal function at the beginning of treatment with NSAID.

4.6. Pregnancy and breastfeeding

Pregnancy

Malformative aspect: 1st trimester

Studies in animals have not shown any teratogenic effect.
In the absence of teratogenic effect in animals, a malformative effect in the human species is not expected. Indeed, so far, the substances responsible for malformations in the human species have proved teratogenic in animals in well-conducted studies on 2 species.

In the human species, no particular malformative effect has been reported. However, further epidemiological studies are needed to confirm the absence of risk.

Fetotoxic and neonatal appearance: 2nd and 3rd trimester

This is a class toxicity for all prostaglandin synthesis inhibitors.
The administration during the 2nd and 3rd quarter exposes to:

- renal functional impairment:

o in utero can be observed from 12 weeks of amenorrhea (start of fetal diuresis):
oligoamnios (most often reversible upon discontinuation of treatment), even anamnios especially during prolonged exposure.
o at birth, renal insufficiency (reversible or not) may persist especially in case of late and prolonged exposure (with a risk of delayed severe hyperkalemia).

- a risk of cardiopulmonary involvement:

o Partial or complete in utero constriction of the ductus arteriosus. The constriction of the may occur after 5 months and may lead to fetal or neonatal right heart failure or even fetal death in utero. This risk is even more important when the intake is close to the term (less reversibility). This effect exists even for a punctual intake.

- a risk of increased bleeding time for the mother and the child.

Consequently:

- Up to 12 weeks of amenorrhea: use of FELDENE should be considered only in case of absolute necessity.

- Between 12 and 24 weeks of amenorrhea (between the beginning of fetal diuresis and 5 months of age): a brief intake should be prescribed only if necessary. Prolonged intake is strongly discouraged.
- Beyond 24 weeks of amenorrhea (5 months of age): any intake, even punctual is contraindicated (see section 4.3). An accidental intake beyond 24 weeks of amenorrhea (5 months) justifies cardiac and renal, fetal and / or neonatal monitoring according to the term of exposure. The duration of this monitoring will be adapted to the elimination half-life of the molecule.

Allaitement

NSAIDs pass into breast milk; as a precaution, they should be avoided in women who are breastfeeding.

4.7. Effects on ability to drive and use machines

Warn patients of the possible occurrence of dizziness and drowsiness.

4.8. Side effects

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (especially when used at high doses and over a long period of time) may be associated with a small increase in the risk of arterial thrombotic events (eg, infarction myocardium or cerebrovascular accident).

The most commonly observed side effects are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal haemorrhage that can sometimes be fatal can occur especially in the elderly. Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, ulcerative stomatitis, abdominal pain, melena, hematemesis, exacerbation of ulcerative colitis or Crohn's disease have been reported following administration of NSAIDs. Gastritis has been observed less frequently.
Edema, hypertension and heart failure have been reported in combination with NSAID therapy.

Gastrointestinal effects:

Gastrointestinal disorders have been reported: anorexia, epigastric heaviness, nausea, vomiting, constipation, abdominal pain, flatulence, diarrhea, ulcers, perforation, occult or non occult digestive haemorrhage. These are all the more frequent as the dosage used is high.
Hypersensitivity reactions:

· Dermatological: rash, pruritus, aggravation of chronic urticaria.

· Respiratory: the onset of asthma attack has been observed in some subjects, particularly in those allergic to aspirin and other nonsteroidal anti-inflammatory drugs.

· General: anaphylaxis, angioedema, vasculitis, serum sickness have been reported exceptionally.

Effects on the central nervous system:

· Headache, drowsiness and dizziness have been reported, as well as tinnitus.

· Isolated cases of hearing loss have been reported.

· Eye disturbances have not been reported during routine ophthalmic examinations and slit lamp tests.

Cutaneous and mucosal reactions:

· Stomatitis.

· Rash, pruritus, rare cases of photosensitization.

· There have been rare reports of bullous skin reactions such as erythema multiforme, ectodermosis pluriorificialis or epidermal necrolysis (Stevens-Johnson, Lyell).

Other:

· Edema, especially lower limbs.

· Sodium and water retention, hyperkalemia.

· Functional acute renal failure (ARF) in patients with risk factors.

· Organic kidney damage that can result in ARF: isolated cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome, papillary necrosis have been reported.

· Exceptional cases of pancreatitis.

Some rare biological modifications have been observed:

· Renal: reversible increase in blood urea and serum creatinine levels.

· Hematologic:

o Decreased platelet aggregation and increased bleeding time, decreased rates of hemoglobin and hematocrit without obvious association with gastrointestinal bleeding.

o Exceptional case of hemolytic anemia.

o Thrombocytopenia and non-thrombocytopenic purpura (Schönlein-Henoch), leukopenia and eosinophilia.

o Rare cases of medullary aplasia.

· Hepatic: Some cases of often transient or reversible changes of liver parameters (serine transaminases, bilirubin) could be observed. More severe liver injury (jaundice, severe or fatal hepatitis) has been reported with piroxicam. If liver function abnormalities persist or worsen or if clinical signs of liver failure or general manifestations (eosinophilia, rash) occur, piroxicam should be discontinued.

· Positive antinuclear antibody test: few anecdotal cases have been reported.

4.9. Overdosage

. Immediate transfer to hospital.

· Rapid evacuation of the product ingested by gastric lavage.

. Activated carbon to reduce the reabsorption of piroxicam and thus reduce serum levels.

· Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

NON-STEROIDAL ANTI-INFLAMMATORY DRUG
(M: locomotor system)

Piroxicam is a nonsteroidal anti-inflammatory drug of the oxicam group. It has the following properties:
· Analgesic activity,
· Antipyretic activity,
· Anti-inflammatory activity,
· Inhibition of platelet function.
All of these properties are related to an inhibition of prostaglandin synthesis.

5.2. Pharmacokinetic properties

The pharmacokinetics of piroxicam is linear. Various studies have shown that there is no change in the pharmacokinetics of piroxicam as a function of age.
Tablet and the capsule forms are bioequivalent.

Absorption

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Piroxicam is rapidly absorbed when administered orally (half-life of resorption: 50 minutes). The overall bioavailability and the importance of absorption are not modified by the diet, the latter slightly delays the rate of absorption.

Distribution

Elimination half-life: about 50 hours.
After oral administration of a tablet of piroxicam 20 mg, a Cmax of 1.85 µg / ml is obtained in 1 hour (Tmax) and 3.72 µg / ml in 1 hour (Tmax) is obtained after administration of 40 mg. Plasma protein binding is important: about 99 percent. Piroxicam rapidly crosses the synovial membrane; synovial levels are, on average, 45 to 50 percent of blood levels. Synovial fluid protein binding is the same as plasma protein binding.
A preliminary study has shown that piroxicam is present in breast milk (approximately 1 to 3% of plasma levels).

Metabolism - Excretion:

Piroxicam is eliminated slowly. It is almost completely metabolized.
Less than 5 percent of the ingested dose is eliminated while being unchanged in the urine and faeces.
Piroxicam is metabolized primarily by cytochrome P450 CYP2C9 in the liver. One of the important metabolic pathways is hydroxylation of the pyridine ring of the piroxicam side-chain, followed by glycuro-conjugation and urinary excretion.

The serum levels monitored after one year of continuous oral administration of 20 mg / day of piroxicam are equivalent to those of the steady state initially reached. One study evaluated the pharmacokinetics of piroxicam at a single dose of 20 mg in healthy volunteers with CYP2C9 * 1 / * 1, CYP2C9 * 1 / * 2 or CYP2C9 * 1 / * 3 genotype. During this study, an increase in AUC0-∞ and a decrease in oral clearance of piroxicam were observed in subjects with genotype CYP2C9 * 1 / * 2 or CYP2C9 * 1 / * 3. An increase in the inhibition of Cyclooxygenase I by piroxicam has also been observed for these same patients.

Piroxicam should be given with caution to patients known or suspected to be poor CYP2C9 metabolizers (based on prior history / experience with other CYP2C9 substrates) because there may be abnormally high levels of piroxicam in the plasma due to decreased metabolism.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Carboxymethylstarch sodium

Cellulose, Microcrystalline
Anhydrous colloidal silica
Magnesium Stearate

6.2. incompatibility

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Keep away from heat and moisture.

6.5. Nature and contents of the outer packaging

Blister in PVC / Alu.

6.6. Special precautions for disposal and handling

No special requirements.

7. HOLDER OF THE MARKETING AUTHORIZATION

Les laboratoires MediS
Route de Tunis – Km 7 – BP 206 – 8000 Nabeul – Tunisie

8. MARKETING AUTHORIZATION NUMBER (S)

9233113

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10. DATE OF REVISION OF THE TEXT

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