FELDENE DISPERSIBLE 20 mg, scored tablet.
Piroxicam

Date : August 2021. Version n° 9

Reference market : France

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

FELDENE DISPERSIBLE 20 mg, scored dispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Piroxicam…… 20.0 mg

For one tablet.

Excipients with known effect: lactose, sodium.

This medicine contains less than 1 mmol sodium (23 mg) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored dispersible tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Piroxicam is indicated for the symptomatic treatment of arthritis, rheumatoid polyarthritis or ankylosing spondylitis. Because of its tolerance profile (see sections 4.2, 4.3 and 4.4), piroxicam must not be used as a first-line treatment when treatment with NSAIDs is indicated.

The decision to prescribe a product containing piroxicam should be based on evaluation of the totality of each patient's specific risks (see sections 4.3 and 4.4).

4.2. Posology and method of administration

Posology

Prescription of products containing piroxicam should be initiated by doctors experienced in the diagnosis and treatment of patients with inflammatory or degenerative rheumatic diseases.

The maximum recommended daily dose is 20 mg.

The onset of side effects can be minimised by using the lowest possible dose necessary to relieve symptoms during the shortest possible treatment period. The benefits and safety of using the treatment should be re-evaluated within 14 days. If it is necessary to continue the treatment, it should be re-evaluated frequently.

If the use of piroxicam is associated with increased risk of gastrointestinal complications, treatment to protect the gastric mucosa (e.g. misoprostol or proton pump inhibitors) should be seriously considered, especially in elderly patients.

Frequency of administration

The tablet should be taken during a meal.

Slow CYP2C9 metabolisers

Given the risk of dose-dependent side effects, it is advisable to administer piroxicam with caution to patients who are known to be or suspected of being slow CYP2C9 metabolisers, based on case histories/previous experience with other CYP2C9 substrates. A dose reduction should be considered (see section 5.2).

Method of administration

Oral use.

The tablet should be swallowed as is or dissolved in a large glass of water.

4.3. Contraindications

This medicinal product is contraindicated in the following situations:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- pregnancy, from the start of the 6th month (beyond 24 weeks of amenorrhoea) (see section 4.6),
- history of allergy or asthma triggered by taking piroxicam or substances with similar activity such as other NSAIDs, aspirin,
- history of serious allergic reactions to medicines of any type, in particular cutaneous reactions such as polymorphous erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome),
- history of ulcers, haemorrhage or gastrointestinal perforation,
- patients with a history of gastrointestinal disorders predisposing them to haemorrhagic disorders such as haemorrhagic rectocolitis, Crohn's disease, gastrointestinal cancers or diverticulitis,
- patients with ongoing peptic ulcer, an inflammatory gastrointestinal disorder or gastrointestinal haemorrhage,
- severe hepatocellular impairment,
- severe heart failure,
- severe renal impairment,
- children under 15 years of age,
- aortocoronary bypass surgery,
- in combination with mifamurtide (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

The concomitant use of piroxixam with other NSAIDs, including cyclooxygenase 2 (cox-2) selective inhibitors, should be avoided.

The onset of side effects can be minimised by using the weakest possible dose for the shortest possible treatment period needed for relief of symptoms (see section 4.2 and the paragraphs on "Gastrointestinal manifestations "and "Cardiovascular and cerebrovascular effects "below).

The clinical benefit and the safety of use should be re-evaluated periodically. Treatment should be stopped immediately at the first sign of cutaneous reaction or symptomatic gastrointestinal events.

Patients with asthma associated with chronic rhinitis, chronic sinusitis and/or nasal polyposis have a higher risk than the general population of allergic events when they take aspirin and/or non-steroidal anti-inflammatories.

Administration of this medicine can trigger an asthmatic crisis, especially in certain subjects who are allergic to aspirin or an NSAID (see section 4.3).

Gastrointestinal (GI) manifestations: risk of ulcers, haemorrhages and GI perforation

NSAIDs, including piroxicam, may trigger serious gastrointestinal side effects, especially haemorrhage, gastric ulcers and perforations, in the small intestine or large intestine, some of which can be fatal. Administration of doses greater than 20 mg per day increases the risk of gastrointestinal side effects. Studies have suggested that piroxicam may be associated

with a higher risk of severe gastrointestinal toxicity than other NSAIDs. These serious side effects can arise at any time, not necessarily with warning signs, in any patient treated with NSAIDs.

Regardless of the duration, any treatment with NSAIDs increases the risk of serious GI side effects.

Patients presenting risk factors for serious GI side effects should only be treated with piroxicam after a detailed evaluation of the risk/benefit ratio (see section 4.3 and below).

The possibility of using a treatment that protects the gastric mucosa (e.g. misoprostol or proton pump inhibitors) should be seriously considered (see section 4.2).

Serious GI complications

Identification of patients at risk

The incidence of serious GI complications increases with age. An increased risk of complications exists for patients over 70 years of age. Administration to patients aged over 80 years of age should be avoided.

Patients receiving concomitant treatments such as oral corticoids, selective serotonin reuptake inhibitors (SSRI) or platelet antiaggregants such as low doses of acetylsalicylic acid have an increased risk of serious GI complications (see below and section 4.5), in the same way as with patients consuming alcohol. As with other NSAIDs, the use of piroxicam in association with gastric mucosal protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for patients at risk.

Both patients and doctors must be vigilant in detecting possible signs and symptoms of ulcers and/or gastric haemorrhage in the course of piroxicam treatment. 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. A complementary clinical evaluation and alternative treatments should be considered.

Cardiovascular (CV) and cerebrovascular effects

Appropriate monitoring and specific recommendations are applicable to patients with a history of hypertension and/or mild to moderate heart failure, as cases of water/salt retention and oedema have been reported in association with NSAIDs.

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (especially at high doses and long term) can be associated with a slight increase in the risk of potentially fatal arterial thrombotic events (for example, myocardial infarction or cerebrovascular accident). The increase in relative risk appears to be similar in all patients, whether or not they present with CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors for CV disease may have a higher risk in terms of absolute impact, due to the higher initial risk. Currently available data are insufficient to rule out this increase in risk with piroxicam.

Patients with uncontrolled hypertension, congestive heart failure, ischaemic cardiopathy, peripheral arterial disease, and/or a history of cerebrovascular accidents (including transitory ischaemic accidents) should only be treated with piroxicam after a careful evaluation of the risk/benefit ratio.

Patients with CV disease may be at an increased risk of aggravation of heart failure. Doctors and patients should be warned of this risk, even in the absence of previous CV symptoms. Patients must also be informed of the signs and symptoms of severe cardiac toxicity and the actions to be taken if they occur (see section 4.3).

The same attention is required before initiating any long-term treatment in patients presenting risk factors for cardiovascular pathology (such as hypertension, hyperlipidaemia, diabetes or tobacco use).

Hypertension

As with all NSAIDs, piroxicam may cause the onset of high blood pressure, or an increase of existing hypertension, which can contribute to an increased incidence of cardiovascular effects. NSAIDs, including piroxicam, should be used with caution in hypertensive patients. Blood pressure should be monitored closely the start of treatment and throughout its duration.

Hepatic reactions

Severe liver disease (jaundice, severe or fatal hepatitis) have rarely been reported with piroxicam. If abnormalities in hepatic function persist or become worse, or if clinical signs of hepatic impairment or general signs (eosinophilia, rash) arise, treatment with piroxicam must be discontinued.

Skin reactions

Serious skin reactions, some of which have fatal outcomes, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome), have been reported in very rare cases in association with NSAID treatment (see section 4.8). Cases of fixed drug eruption (FDE) have been reported with piroxicam. Piroxicam should not be reintroduced in patients with history of piroxicam-related FDE. Potential cross reactivity might occur with other oxicams.
Studies have suggested that piroxicam could be associated with an increased risk of serious cutaneous reactions compared to other NSAIDs that are not oxicam derivatives. The incidence of these side effects seems to be more significant at the start of treatment, in the majority of cases during the first month of treatment. Treatment with piroxicam should be stopped upon appearance of a cutaneous rash, mucosal lesions or any other sign of hypersensitivity.

Functional renal impairment

By inhibiting the vasodilator action of renal prostaglandins, NSAIDs can trigger functional renal impairment by decreasing glomerular filtration.

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

- elderly patients,
- medicines administered concomitantly, such as: ACE inhibitors, ARBs, diuretics (see section 4.5),
- hypovolaemia, regardless of the cause,
- heart failure,
- chronic renal impairment,
- nephrotic syndrome,
- lupus nephritis,
- decompensated hepatic cirrhosis.

Particular attention must be paid upon starting treatment with piroxicam in patients with severe dehydration. Monitoring is also recommended in patients with renal impairment (see section 4.3)

Because of the substantial elimination of piroxicam and its biotransformation products by the kidneys, lower doses of piroxicam should be considered in patients with impaired renal function, and these patients should be closely monitored (see sections 4.3 and 5.2).

Use with oral anticoagulants

The concomitant use of NSAIDs, including piroxicam, with oral anticoagulants increases the risk of gastrointestinal and non-gastrointestinal bleeding and should be avoided. Oral anticoagulants include warfarin anticoagulants/coumarin and direct oral anticoagulants (for example apixaban, dabigatran, rivaroxaban). Anticoagulation/the INR should be monitored in patients taking warfarin/coumarin-type anticoagulants (see section 4.5).

Fluid retention

Water/salt retention with possible oedema, hypertension or increased hypertension, exacerbation of heart failure. Clinical monitoring is necessary at the beginning of treatment in case of hypertension or heart failure. A decrease in the effect of antihypertensive medicines is possible (see section 4.5).

Hyperkalaemia

Hyperkalaemia caused by diabetes or treatment with hyperkalaemiant medicines (see section 4.5).

Regular monitoring of blood potassium level is necessary under these circumstances.

Elderly patients

Elderly patients have an increased risk of side effects to NSAIDs, in particular gastrointestinal haemorrhage and perforations, which can be fatal (see section 4.2).

In prescribing, the doctor should take into account the fact that cases of secondary anovulatory infertility caused by non-rupture of the De Graaf follicle, reversible when treatment is stopped, have been described in patients receiving long-term treatment with certain prostaglandin synthesis inhibitors.

Excipients

This medicinal product contains lactose. Patients with galactose intolerance, total lactase deficiency, or malabsorption of glucose and galactose syndrome (rare hereditary diseases) should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Precautions for use

This medicine is available in other dose forms that may be more appropriate.

The onset of an asthma crisis in certain patients may be linked to an allergy to aspirin or to NSAIDS (see section 4.3).

Suitable monitoring is necessary for patients with a history of hypertension and/ heart failure, as cases of water/salt retention and oedema have been reported in connection with NSAID treatment.

Poor metabolisers of CYP2C9 substrates

Piroxicam should be administered to patients known or suspected to be poor metabolisers of CYP 2C9 with caution, based on previous experience with other CYP2C9 substrates, as abnormally high plasma concentrations of piroxicam may occur due to its decreased metabolism (see section 5.2).

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

Simultaneous administration of piroxicam with the following products requires rigorous monitoring of the patient's clinical and biological state.

Contraindicated combinations

+ **Mifamurtide**

At high doses of NSAIDs, risk of less effective mifamurtide.

Inadvisable combinations

+ **Acetylsalicylic acid at anti-inflammatory doses (≥1 g per dose and/or ≥3 g per day) or at analgesic or antipyretic doses (≥500 mg per dose and/or <3 g per day)**

Increased risk of digestive ulcers and haemorrhage.

+ **Oral anticoagulants**

NSAIDs, including piroxicam, are likely to enhance the effects of anticoagulants, such as coumarin-type derivatives (warfarin) and direct oral anticoagulants (for example, apixaban, dabigatran, rivaroxaban). Increase in the risk of haemorrhage from oral anticoagulant (aggression of the gastroduodenal mucosa by non-steroidal anti-inflammatories). Consequently, the concomitant use of piroxicam and anticoagulants should be avoided. If the association cannot be avoided, carry out close clinical, or even biological, monitoring (see section 4.4).

+ **Other non-steroidal anti-inflammatories (including aspirin and other salicylates)**

With other non-steroidal anti-inflammatories: increased risk of digestive ulcers and bleeding.

As with all NSAIDs, the use of piroxicam combined with acetylsalicylic acid or other NSAIDs, and the combination of several proprietary medicinal products containing piroxicam, must be avoided. No data has made it possible to demonstrate the benefit of these combinations compared with piroxicam alone, and therefore the incidence of adverse effects is increased (see section 4.4).

Human studies have highlighted a reduced piroxicam plasma concentration of approximately 80% of the usual value during the concomitant administration of piroxicam and acetylsalicylic acid.

+ **Heparins of low molecular weight and related substances (curative doses and/or elderly patients)**

Increased risk of bleeding for oral anticoagulants (aggression of the gastroduodenal mucosa by non-steroidal anti-inflammatories). If the combination cannot be avoided, ensure close clinical monitoring.

+ **Unfractionated heparins (curative doses and/or elderly patients)**

Increased risk of bleeding for oral anticoagulants (aggression of the gastroduodenal mucosa by non-steroidal anti-inflammatories). If the combination cannot be avoided, ensure close clinical monitoring.

+ **Lithium**

Increase of lithaemia that can reach toxic levels (decrease in the renal excretion of lithium).

If the combination cannot be avoided, closely monitor lithium levels and adapt the lithium dose both during concomitant treatment and after stopping the non-steroidal anti-inflammatories.

+ **Methotrexate administered at doses greater than 20 mg/week**

Increase in haematological toxicity for methotrexate (decreased renal elimination of methotrexate with anti-inflammatories).

+ **Nicorandil**

Increased risk of digestive ulcers and bleeding.

+ **Pemetrexed (in patients with mild to moderate renal function):**

Risk of increasing the toxicity of pemetrexed (decrease in renal clearance caused by NSAIDs).

Combinations requiring precautions for use

+ **Angiotensin II receptor antagonists**

Acute renal impairment in at-risk patients (elderly, dehydration, concomitant treatment with diuretics, renal function impairment), due to decreased glomerular filtration secondary to a decrease in synthesis of renal prostaglandins. These effects are usually reversible. In addition, reduction of the anti-hypertensive effect.

Hydrate the patient and monitor renal function at baseline and periodically throughout the combination.

+ **Ciclosporin**

Risk of additional nephrotoxic effects, particularly in elderly subjects.

Monitor renal function at the beginning of treatment with NSAIDs.

+ Cobimetinib

Increased haemorrhagic risk.

Clinical monitoring.

+ **Diuretics**

Acute renal failure in at-risk the patient (elderly, dehydrated, on diuretics, with impaired renal function) by decreasing glomerular filtration secondary to a decrease in synthesis of renal prostaglandins. These effects are usually reversible. In addition, reduction of the anti-hypertensive effect.

Hydrate the patient and monitor renal function at the start of treatment and regularly during the combination.

+ **Angiotensin-converting enzyme inhibitors**

Acute renal failure in at-risk patient (elderly, dehydrated, diuretic-treated, impaired renal function), due to decreased glomerular filtration secondary to a decrease in synthesis of renal prostaglandins. These effects are generally reversible. In addition, reduction of the anti-hypertensive effect.

Hydrate the patient and monitor renal function at baseline and periodically throughout the combination.

+ **Methotrexate, used at low doses (lower than or equal to 20 mg/week)**

Increase in haematological toxicity for methotrexate (decreased renal elimination of methotrexate with anti-inflammatories).

Weekly monitoring of the CBC during the first weeks of the combination. Increased monitoring in case of changes (even slight) in renal function as well as for elderly patients.

+ **Pemetrexed in patients with normal renal function**

Risk of increasing the toxicity of pemetrexed (decrease in renal clearance caused by NSAIDs).

Biological monitoring of renal function.

+ **Tacrolimus**

Risk of additional nephrotoxic effects, particularly in elderly patients.

Renal function should be monitored at the start of treatment with NSAIDs.

+ **Tenofovir disoproxil**

Risk of increased nephrotoxicity due to tenofovir, particularly with high doses of the anti-inflammatory or in the presence of risk factors for renal impairment.

When used in combination, renal function should be monitored.

Combinations to be taken into account

+ **Acetylsalicylic acid at anti-aggregating doses (from 50 mg to 375 mg per day in one or more doses)**

Increased risk of gastrointestinal ulcers and haemorrhage.

Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect must be taken into account when determining the bleeding time.

Piroxicam interferes with the anti-platelet effect of aspirin at low doses, and may therefore interfere with the prophylactic effect of aspirin in the treatment of CV disease.

+ **Platelet anti-aggregants**

Increased risk of bleeding, especially gastrointestinal.

+ **Other potassium-sparing agents**

Risk of potentially fatal increase in hyperkalaemia.

Risk related to hyperkalaemia

Certain medicines or therapeutic classes may predispose patients to the occurrence of hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, non-steroidal anti-inflammatory agents, heparin (low molecular weight or unfractionated), immunosuppressants such as ciclosporin or tacrolimus, trimethoprim.

The combination of these medicines increases the risk of hyperkalaemia. This risk is particularly significant with potassium-sparing diuretics, especially when combined with each other or with potassium salts, whereas the combination of an ACE inhibitor and an NSAID, for example, is safer provided the recommended precautions are taken.

To learn more about the risks and restriction levels of specific potassium-sparing agents, physicians should refer to the interactions specific to each substance.

However, some substances, such as trimethoprim, are not subject to specific interactions in relation to this risk. Nevertheless, they may act as predisposing factors when combined with other medicines already mentioned in this section.

Onset of hyperkalaemia can depend on the presence of co-associated factors.

+ **Beta blockers (except esmolol) (including eye drops)**

Reduction in the antihypertensive effect (inhibition of vasodilator prostaglandins by non-steroidal anti-inflammatories).

+ **Deferasirox**

Increased risk of digestive ulcers and haemorrhage.

+ **Glucocorticoids (except hydrocortisone)**

Increased risk of gastrointestinal ulcers and haemorrhage (see section 4.4).

+ **Unfractionated heparins and low-molecular weight heparins and related (prophylactic doses)**

Increased risk of haemorrhage.

+ **Selective serotonin reuptake inhibitors (SSRI)**

Increased risk of haemorrhage (see section 4.4).

+ Mixed adrenergic-serotonergic drugs

Increased haemorrhagic risk.

4.6. Fertility, pregnancy and breast-feeding

Pregnancy

Inhibition of prostaglandin synthesis by NSAIDs may affect the course of pregnancy and/or the development of the embryo or foetus.

Risks related to the use during the 1st trimester

Data of epidemiological studies suggests an increase in the risk of miscarriage, heart malformations and gastroschisis, after treatment by a prostaglandin synthesis inhibitor at the start of pregnancy. The absolute risk of cardiovascular malformations went from less than 1% in general population to approximately 1.5% in people exposed to NSAIDs. The risk appears to increase with dose and treatment duration. In animals, it has been shown that the administration of a prostaglandin synthesis inhibitor causes an increased risk of pre- and post-implant loss and a rise in embryo-foetal fatality. Moreover, a higher incidence of certain malformations, including cardiovascular malformations, has been reported in animals who received a prostaglandin synthesis inhibitor during the organogenesis phase of gestation.

Risks related to the use from the 12th week of amenorrhoea and until birth:

- From the 12th week of amenorrhoea and until birth, all NSAIDs, by inhibition of prostaglandin synthesis, may expose the foetus to **renal function disorder:**
  - *in utero* observed from 12 weeks of amenorrhoea (start of foetal diuresis): oligoamnios (usually reversible after discontinuation of treatment), or anamnios, especially after extended exposure.
  - at birth, renal impairment (reversible or irreversible) can persist, particularly in case of late and prolonged exposure (with a risk of severe delayed hyperkalaemia).

Risks related to the use from the 24th week of amenorrhoea and until birth:

From the 24th week of amenorrhea, NSAIDs may expose the foetus to **cardiopulmonary toxicity** (premature closure of the ductus arteriosus and pulmonary arterial hypertension). Constriction of the arterial canal may arise from the beginning of the 6th month (beyond the 24th week of amenorrhoea), and can lead to foetal or neonatal right heart failure or foetal death *in utero*. This risk is greater the closer administration is to delivery (less reversibility). This effect occurs even with occasional administration.

At the end of pregnancy, the mother and newborn may have:

- increased bleeding time due to an anti-aggregating action, which may arise even after the administration of very small doses of the medicinal product;
- an inhibition of uterine contractions, resulting in a delay in term or prolonged delivery.

Consequently:

Unless absolutely necessary, this medicinal product must not be prescribed in a woman considering pregnancy or during the first 5 months of pregnancy (first 24 weeks of amenorrhoea). If this medicinal product is administered to a woman intending to get pregnant or who is less than 6 months pregnant, the dose should be as low as possible and the duration of treatment as short as possible. Prolonged use is highly inadvisable.

From the beginning of the 6th month (after 24 weeks of amenorrhoea): any ongoing administration, however brief, is contraindicated. An inadvertent use from this date requires

cardiac and renal monitoring of the foetus or neonate, depending on the date of exposure. The duration of this monitoring depends on the elimination half-life of the molecule.

Breast-feeding

Because NSAIDs pass into breast milk, this medicinal product is not recommended for use by breast-feeding women.

Fertility

Like all NSAIDs, the use of this medicinal product may temporary affect female fertility by acting on ovulation. It is therefore not recommended for women wishing to conceive a child. In women having difficulty conceiving or undergoing fertility tests, discontinuation of treatment should be considered.

4.7. Effects on ability to drive and use machines

Warn patients of possible vertigo or drowsiness.

4.8. Undesirable effects

Clinical studies and epidemiological data suggest that the use of certain NSAIDs (especially at high doses and long term) can be associated with a slight increase in the risk of arterial thrombotic events (for example, myocardial infarction or cerebrovascular accident) (see section 4.4).

The most frequently observed side effects are gastrointestinal in nature. Peptic ulcers, gastrointestinal perforations or haemorrhages, sometimes fatal, can occur, especially in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, ulcerative stomatitis, abdominal pain, melaena, haematemesis, aggravation of rectocolitis or Crohn's disease (see section 4.4) have been reported after administration of NSAIDs. Less frequently, gastritis has been observed.

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

Gastrointestinal effects

Gastrointestinal disorders have been reported, including anorexia, epigastric heaviness, nausea, vomiting, constipation, abdominal pain, flatulence, diarrhoea, ulcers, perforations, gastrointestinal bleeding (occult or otherwise), abdominal discomfort, abdominal pain, anorectal reaction upon administration of suppositories, characterised by local pain, burns, pruritus and occasional tenesmus and rectal bleeding, epigastric pain, gastritis, gastrointestinal bleeding (including haematemesis and melaena), indigestion. The frequency of occurrence for these effects is directly proportional to the dose (see section 4.4).

Hypersensitivity reactions

- Dermatological: eruption, rash, pruritus, exacerbation of chronic hives, alopecia,
- Respiratory: onset of an asthma crisis, bronchospasm and dyspnoea were observed in certain patients, particularly those allergic to aspirin and other non-steroidal anti-inflammatories,
- General: nosebleeds, anaphylaxis, Quincke's oedema, vascularitis, hypertension, serum disorders were very rarely reported.

Effects on the central nervous system

- Headache, drowsiness, dizziness, aseptic meningitis, dizziness and paraesthesia have been reported, as well as tinnitus,
- Isolated cases of decreased auditory acuity were reported very rarely,
- There were no reports of ocular disturbances in eye exams, or in routine checks using a slit lamp (blurred vision, eye irritation, eye swelling).

Mucosa and skin reactions

- Stomatitis,
- Eruptions, pruritus, rare cases of photosensitisation,
- Rare cases have been reported of bullous skin reactions of erythema multiforme, ectodermose of multi-orificial type or epidermal necrolysis type (Stevens-Johnson syndrome, Lyell's syndrome), angioedema, exfoliative dermatitis, erythema multiforme, onycholysis, DRESS syndrome, fixed drug eruption - frequency unknown (see section 4.4).

Renal and urinary effects

- Acute renal failure (ARF) in patients presenting risk factors (see section 4.4).
- Organic kidney disease may result in acute renal failure: isolated cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome and papillary necrosis have been reported.

Other

- Oedema, in particular of the legs, local reactions (burning sensations) or tissue damage (formation of sterile abscesses, adipose tissue necrosis) at the injection site, malaise, transient pain upon injection.
- Water/salt retention, hyperkalaemia (see sections 4.4 and 4.5).
- Exceptional cases of pancreatitis.

Some rare biological modifications have been observed

- Renal: reversible elevation of the blood urea and creatinine concentrations.
- Haematological:
  - Decrease of platelet ability to aggregate and extended bleeding time, decrease in the haemoglobin concentration and the hematocrit not associated with obvious gastrointestinal bleeding,
  - Exceptional cases of haemolytic anaemia,
  - Thrombocytopenia and non-thrombocytopenic purpura (Schönlein-Henoch), leukopenia and eosinophilia,
  - Rare cases of medullary aplasia.
- Hepatic: some cases, most often transitory or reversible, of modification of the hepatic parameters (serum transaminases, bilirubin) have been observed. Severe hepatic disorder (icterus, serious or fatal hepatitis) was reported as a rare exception with piroxicam. In case of persistence or aggravation of liver anomalies, or occurrence of clinical symptoms of hepatic impairment or general symptoms such as eosinophilia or rash, the piroxicam should be stopped.
- Positive antinuclear antibody test: a few anecdotal cases have been reported.
- Metabolism and nutrition disorders: Hyperglycaemia, hypoglycaemia, fluid retention.
- Cardiac disorders: palpitations.
- Reproductive system and breast disorders, decreased female fertility.

Reporting of suspected side effects

The reporting of side effects 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 side effects via the national reporting system.

4.9. Overdose

- Immediate transfer to a hospital.
- Rapid evacuation of the ingested product by gastric lavage.

- Activated charcoal to decrease the reabsorption of piroxicam and thus reduce its serum concentration.
- Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: NON-STEROIDAL ANTI-INFLAMMATORY, ATC code: M01AC01.

Piroxicam is a non-steroidal anti-inflammatory in the oxicam group. It has the following properties:

- analgesic action,
- antipyretic action,
- anti-inflammatory activity,
- Inhibitory action on platelet function.

All these properties are linked to inhibition of prostaglandin synthesis.

5.2. Pharmacokinetic properties

The pharmacokinetics of piroxicam are linear. Various studies have shown that the pharmacokinetics of piroxicam are not modified with the patient's age. The gel capsules and tablets are bioequivalent.

Absorption

Administered orally, piroxicam is rapidly absorbed (absorption half-life: 50 minutes).

The overall bioavailability and the degree of absorption are not modified by food, although food delays the absorption rate slightly.

Distribution

The elimination half-life: approximately 50 hours.

After oral administration of a 20 mg piroxicam gel capsule, the C_{max} is 1.85 µg/mL in 1 hour (T_{max}) and 3.72 µg/mL in 1 hour (T_{max}) after administration of 40 mg.

Binding to plasma proteins is significant: approximately 99%.

Piroxicam passes over the synovial membrane rapidly: synovial concentrations are, on average, 45 to 50% of blood concentrations.

Binding to synovial fluid proteins is the same as the binding to plasma proteins.

A preliminary study has shown that piroxicam is present in breast milk (approximately 1 to 3% of plasma concentration).

Biotransformation - Elimination

Piroxicam is eliminated slowly. It is almost completely metabolised.

Less than 5% of the ingested dose is eliminated unchanged in the urine and faeces.

Piroxicam is primarily metabolised by cytochrome P450 CYP 2C9 in the liver. One of the important metabolic pathways is hydroxylation of the pyridyl group in the side chain of piroxicam, followed by glycuro conjugation and elimination in the urine.

The serum concentration measured after one year of continuous oral administration of 20 mg/day of piroxicam are equivalent to those of the equilibrium originally attained.

One study evaluated the pharmacokinetics of piroxicam administered as single dose of 20 mg to healthy volunteers presenting a CYP2C9*1/*1, CYP2C9*1/*2, or CYP2C9*1/*3

genotype. During the study, an increase in and a reduction in oral clearance of prioxicam was seen in subjects with CYP2C9*1/*2 or CYP2C9*1/*3 genotype. An increase in inhibition of Cyclooxygenase I by piroxicam was also observed for these patients.

It is advisable to administer piroxicam with caution to patients who are known to be or suspected of being slow CYP2C9 metabolisers, as an abnormally high plasma piroxicam concentration may occur due to decreased metabolism (see section 4.4).

Pharmacogenetics

The activity of CYP2C9 is decreased in individuals with certain genetic polymorphisms, for example the polymorphisms CYP2C9*2 and CYP2C9*3. Limited data from two published reports have shown that subjects with heterozygous genotypes CYP2C9*1/*2 (n = 9), heterozygous CYP2C9*1/*3 (n = 9) and homozygous CYP2C9*3/*3 (n = 1) had systemic levels of piroxicam respectively 1.7, 1.7 and 5.3 times higher than subjects with the CYP2C9*1/*1 genotype (n = 17, normal metabolisers) following administration of a single oral dose. Mean values for the elimination half-life of piroxicam in patients with genotypes CYP2C9*1/*3 (n = 9) and CYP2C9*3/*3 (n = 1) were respectively 1.7 and 8.8 times higher than those of subjects with the CYP2C9 *1/*1 genotype (n = 17). It is estimated that the frequency of the homozygous *3/*3 genotype is 0 % to 5.7 % across different ethnic groups.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, microcrystalline cellulose (AVICEL), hydroxypropyl cellulose, sodium stearyl fumarate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store away from heat and moisture.

6.5. Nature and contents of the outer packaging

15 tablets in bottle (PE)

6.6. Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Holder
PFIZER HOLDING FRANCE
23-25, AVENUE DU DOCTEUR LANNELONGUE

75014 PARIS

Manufacturer
FAREVA AMBOISE
ZONE INDUSTRIELLE
29 ROUTE DES INDUSTRIES
37530 POCE-SUR-CISSE

Presentation :
FELDENE 20 mg box of 15 tablets in bottle (PE)

Local representative :
Pfizer Afrique de l'Ouest

Administrative address :
Pfizer Afrique de l'Ouest
Regus Plateau 3rd Floor
Azur 15 Building
12 Boulevard Djily Mbaye
Dakar Sénégal BP 3857 Dakar RP

8. CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

List I.

9. DATE OF REVISION OF THE TEXT

18 June 2021.