

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Feldene 10 mg capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules containing 10 mg piroxicam (anhydrous).

Excipients with known effect: Each capsule contains 243.23 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Red cap and blue body, coded 'PFIZER' and 'FEL10'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Feldene is indicated for symptomatic relief of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

Due to its safety profile (*see sections 4.2, 4.3, and 4.4*), Feldene is not a first line option should an NSAID be indicated. The decision to prescribe Feldene should be based on an assessment of the individual patient's overall risks (*see sections 4.3 and 4.4*).

Treatment should only be initiated by specialist clinicians.

4.2 Posology and method of administration

The prescription of Feldene should be initiated by physicians with experience in the diagnostic evaluation and treatment of patients with inflammatory or degenerative rheumatic diseases.

Posology

The maximum recommended daily dose is 20 mg.

Paediatric population

Dosage recommendations and indications for use in children have not been established.

Elderly

Elderly, frail or debilitated patients may tolerate side-effects less well and such patients should be carefully supervised. As with other NSAID's, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. The benefit and tolerability of treatment should be reviewed within 14 days. If continued treatment is considered necessary, this should be accompanied by frequent review.

Given that piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

4.3 Contraindications

- History of gastro-intestinal ulceration, bleeding or perforation.
- Patient history of gastrointestinal disorders that predispose to bleeding disorders such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis.
- Patients with active peptic ulcer, inflammatory gastrointestinal disorder or gastrointestinal bleeding.
- Coadministration of other NSAIDs, including COX-2 selective NSAIDs and acetyl-salicylic acid at analgesic doses.
- Concomitant use with anticoagulants. (see section 4.4 and 4.5).
- History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications.
- Peanut or soya allergy.
- Patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce the symptoms of asthma, rhinitis, angioedema or urticaria.
- Moderate or severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be reduced by using the minimum effective dose for the shortest duration necessary to control symptoms. Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

The clinical benefit and tolerability should be re-evaluated periodically and treatment should be immediately discontinued at the first appearance of cutaneous reactions or relevant gastrointestinal events.

Gastrointestinal (GI) Effects, Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including piroxicam, can cause serious GI adverse events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. NSAID exposures of both short and long duration have an increased risk of serious GI event. Administration of doses of greater than 20 mg per day carries an increased risk of GI side effects. Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

Patients with significant risk factors for serious GI events should be treated with piroxicam only after careful consideration (see sections 4.2, 4.3 and below).

The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered (see section 4.2).

Serious GI Complications

Identification of at-risk subjects

The risk for developing serious GI complications increases with age. Age over 70 years is associated with high risk of complications. The administration to patients older than 80 years should be avoided.

Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs), patients ingesting alcohol or anti-platelet agents such as low-dose acetylsalicylic acid are at increased risk of serious GI complications (see below and section 4.5). As with other NSAIDs, the use of piroxicam in combination with protective agents (e.g. misoprostol or proton pump inhibitors) must be considered for these at-risk patients.

Patients and physicians should remain alerted for signs and symptoms of GI ulceration and/or bleeding during piroxicam treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately and additional clinical evaluation and treatment should be considered.

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.

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

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high dose 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 piroxicam. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

In rare cases, non-steroidal anti-inflammatory drugs may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome. Such agents inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of a non-steroidal anti-inflammatory drug may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of non-steroidal anti-inflammatory therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, such patients should be carefully monitored whilst receiving non-steroidal anti-inflammatory therapy.

Because of reports of adverse eye findings with non-steroidal anti-inflammatory drugs, it is recommended that patients who develop visual complaints during treatment with Feldene have ophthalmic evaluation.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis (see section 4.5).

Skin reactions

Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported with the use of piroxicam.

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, piroxicam 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 piroxicam, piroxicam must not be re-started in this patient at any time.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Epidemiological evidence suggests that piroxicam may be associated with a higher level of risk of serious skin reactions than non-oxicam NSAIDs. Patients appear to be at highest risk of these events early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hepatic Effects

Piroxicam can cause fatal hepatitis and jaundice. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc), piroxicam should be discontinued.

Poor Metabolizers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 5.2).

Use with oral anticoagulants

The concomitant use of NSAIDs, including piroxicam, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be avoided. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (see sections 4.3 and 4.5).

Use in patients with impaired hepatic function: See above

Use in patients with renal impairment: See above

Children: See section 4.2

Use in the elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially GI bleeding and perforation which may be fatal (see section 4.2).

Impaired female fertility

The use of piroxicam may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of piroxicam should be considered.

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

This medicinal product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Aspirin and other NSAIDs: As with other NSAIDs, the use of piroxicam together with acetyl-salicylic acid or concomitant use with other NSAIDs, including other piroxicam formulations, must be avoided, since data are inadequate to show that such combinations produce greater improvement than that achieved with piroxicam alone; moreover, the potential for adverse reactions is enhanced (see section 4.4).

Human studies have shown that concomitant use of piroxicam and acetyl-salicylic acid reduces the plasma piroxicam concentration to about 80% of the usual value.

Piroxicam interferes with the antiplatelet effect of low-dose aspirin, and thus may interfere with aspirin's prophylactic treatment of CV disease.

Anticoagulants: NSAIDs, including piroxicam, may enhance the effects of anti-coagulants, such as warfarin. Therefore, the use of piroxicam with concomitant anticoagulants such as warfarin should be avoided (see section 4.3).

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

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers: NSAIDs can reduce the efficacy of diuretics and other anti-hypertensive drugs including ACE inhibitors, AIIA and beta-blockers.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function including the possibility of acute renal failure, which is usually reversible.

The occurrence of these interactions should be considered in patients taking piroxicam with an ACE inhibitor or an AIIA and/or diuretics. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

NSAIDs may cause sodium, potassium and fluid retention, and may inhibit the natriuretic action of diuretic agents. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension since they may be responsible for a worsening of those conditions.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium.

Methotrexate: When methotrexate is administered concurrently with NSAIDs, including piroxicam, NSAIDs may decrease elimination of methotrexate resulting in increased plasma levels of methotrexate. Caution is advised, especially in patients receiving high doses of methotrexate.

Ciclosporin and tacrolimus: increased risk of nephrotoxicity with NSAIDs.

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

Aminoglycosides: reduction in renal function in susceptible individuals decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs prolonged half-life and increased risk of hypoglycaemia.

Antacids: Concomitant administration of antacids had no effect on piroxicam plasma levels.

Digoxin, digitoxin: Concurrent therapy with Feldene and digoxin, or Feldene and digitoxin did not affect the plasma levels of either drug.

Highly protein bound drugs: Feldene is highly protein-bound, and therefore might be expected to displace other protein-bound drugs. The physician should closely monitor patients for change in dosage requirements when administering Feldene to patients on highly protein-bound drugs.

Cimetidine: Results of two separate studies indicate a slight but significant increase in absorption of piroxicam following cimetidine administration but no significant changes in elimination rate constants or half-life. The small increase in absorption is unlikely to be clinically significant.

4.6 Fertility, pregnancy and lactation

Fertility: Based on the mechanism of action, the use of NSAIDs, including Feldene, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including Feldene, should be considered.

Pregnancy: Although no teratogenic effects were seen in animal testing, the use of piroxicam during pregnancy is not recommended. Feldene inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme. This effect, as with other non-steroidal anti-inflammatory drugs, has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued in late pregnancy. NSAIDS are also known to induce closure of the ductus arteriosus in infants. Therefore, piroxicam should be avoided during the third trimester of pregnancy.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

If used during second or third trimester of pregnancy, NSAIDs may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on piroxicam should be closely monitored for amniotic fluid volume.

Breast-feeding: A study indicates that piroxicam appears in breast milk at about 1% to 3% of the maternal plasma concentrations. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment for up to 52 days. Feldene is not recommended for use in nursing mothers, as clinical safety has not been established.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

| System Organ Class | Very Common ≥1/10 | Common ≥1/100 to <1/10 | Uncommon ≥1/1000 to <1/100 | Rare ≥1/10 000 to <1 000 | Very Rare <1/10000 | Not Known (cannot be estimated from available data) |
|--------------------------------------|----------------------|---|-------------------------------|-----------------------------|-----------------------|--|
| Blood and lymphatic system disorders | | Anaemia Eosinophilia Leucopenia Thrombocytopenia | | | | Aplastic anaemia Haemolytic anaemia |
| Immune system disorders | | | | | | Anaphylaxis Serum sickness |
| Metabolism and nutrition disorders | | Anorexia Hyperglycaemia | Hypoglycaemia | | | Fluid retention |
| Psychiatric disorders | | | | | | Depression Dream abnormalities Hallucinations |

| | | | | | | |
|---|--|---|----------------|--|---|--|
| | | | | | | Insomnia Mental confusion Mood alterations Nervousness |
| Nervous system disorders | | Dizziness Headache Somnolence Vertigo | | | | Paresthesia |
| Eye disorders | | | Blurred vision | | | Eye irritations Swollen eyes |
| Ear and labyrinth disorders | | Tinnitus | | | | Hearing impairment |
| Cardiac disorders | | | Palpitations | | | Cardiac failure Arterial thrombotic events |
| Vascular disorders | | | | | | Vasculitis Hypertension |
| Respiratory, thoracic and mediastinal disorders | | | | | | Bronchospasm Dyspnoea Epistaxis |
| Gastrointestinal disorders | | Abdominal discomfort Abdominal pain Constipation Diarrhoea Epigastric distress Flatulence Nausea Vomiting Indigestion | Stomatitis | | | Gastritis Gastrointestinal bleeding (including hematemesis and melena) Pancreatitis Perforation Ulceration Exacerbation of colitis and Crohn’s disease Ulcerative stomatitis |
| Hepatobiliary disorders | | | | | | Fatal hepatitis Jaundice |
| Skin and subcutaneous tissue disorders | | Pruritis Skin rash | | | Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4) | Alopecia Angioedema Dermatitis exfoliative Erythema multiforme Non-thrombocytopenic purpura (Henoch-Schoenlein) Onycholysis Photoallergic reactions Urticaria Vesiculo bullous reactions |
| Renal and urinary | | | | | | Nephrotic syndrome |

| | | | | | | |
|---|--|---|---|--|--|--|
| disorders | | | | | | Glomerulonephritis Interstitial nephritis Renal failure |
| Reproductive system and breast disorders | | | | | | Female fertility decreased |
| General disorders and administration site conditions | | Oedema (mainly of the ankle) | | | | Malaise |
| Investigations | | Reversible elevations of BUN Increased serum transaminase levels Weight increase | Reversible elevations of creatinine | | | Positive ANA Weight decrease Decreases in hemoglobin and hematocrit unassociated with obvious gastro- intestinal bleeding |

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Objective evaluations of gastric mucosal appearances and intestinal blood loss show that 20mg/day of Feldene administered either in single or divided daily doses is significantly less irritating to the gastro-intestinal tract than aspirin. Peptic ulceration, perforation and gastro-intestinal bleeding (including haematemesis and melaena) in rare cases fatal, particularly in the elderly, have been reported with Feldene (see section 4.4). Long-term administration of doses of 30mg or higher carries an increased risk of gastro-intestinal side-effects.

Elderly patients tend to be more susceptible to gastrointestinal bleeding, and as with other agents, elderly patients should be carefully monitored.

Oedema, hypertension and cardiac failure: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. The possibility of precipitating congestive cardiac failure in elderly patients or those with compromised cardiac function should therefore be borne in mind.

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).

Other: Routine ophthalmoscopy and slit-lamp examination have revealed no evidence of ocular changes.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

In the event of overdosage with Feldene, supportive and symptomatic therapy is indicated. Studies indicate that administration of activated charcoal may result in reduced absorption and reabsorption of piroxicam, thus reducing the total amount of active drug available.

Although there are no studies to date, haemodialysis is probably not useful in enhancing elimination of piroxicam since the drug is highly protein bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: M01AC01 code:

Feldene is a non-steroidal anti-inflammatory agent useful in the treatment of inflammatory conditions. Although the mode of action for this agent is not precisely understood, Feldene inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme.

5.2 Pharmacokinetic properties

Feldene pharmacokinetics are similar following oral or rectal administration. Following oral administration with food, there is a slight delay in the rate, but not the extent, of absorption. The plasma half-life is approximately 50 hours in man and stable plasma concentrations are maintained throughout the day on once-daily dosage. Continuous treatment with 20mg/day for periods of one year produces similar blood levels to those seen once steady state is first achieved.

Feldene is extensively metabolised and less than 5% of the daily dose is excreted unchanged in urine and faeces. Piroxicam metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side chain, followed by conjugation with glucuronic acid and urinary elimination.

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 4.4).

Pharmacogenetics

CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n=9), heterozygous CYP2C9*1/*3 (n=9), and homozygous CYP2C9*3/*3 (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*1 (n=17, normal metabolizer genotype) following administration of an oral single dose. The mean elimination half life values of piroxicam for subjects with CYP2C9*1/*3 (n=9) and CYP2C9*3/*3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9*1/*1 (n=17). It is estimated that the frequency of the homozygous*3/*3 genotype is 0% to 5.7% in various ethnic groups.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate
Magnesium stearate
Maize starch
Sodium laurilsulfate

Capsule Shell

Cap (red): Gelatin
 Titanium dioxide (E171)
 Red iron oxide (E172)

Body (blue): Gelatin
 Titanium dioxide (E171)
 Indigotine (E132)

Printing Ink

Black iron oxide (E172)
Shellac (E904)
Soya lecithin (E322)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Original packs of 30 capsules contained in a white HDPE bottle with a blue round ribbed cap in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0019/024/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 April 1979

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10 DATE OF REVISION OF THE TEXT

July 2017