SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Feldene Melt 20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Piroxicam 20mg.

Excipients with known effect:
Each Feldene Melt 20 mg tablet contains 0.250 mg aspartame.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Fast Dissolving Dosage Form (Tablet)

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).

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 20mg.

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.

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

For oral administration. To be taken preferably with or after food. The fast dissolving dosage form may be swallowed with water, or placed on the tongue to disperse and then swallowed with the saliva. The fast dissolving dosage form dissolves almost instantly in the mouth in the presence of water or saliva.

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

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.

Concomitant use with other NSAIDs, including COX-2 selective NSAIDs and acetyl-salicylic acid at analgesic doses.

Concomitant use with anticoagulants (see section 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.

Patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce the symptoms of asthma, nasal polyps, angioedema or urticaria.

Severe heart failure.

During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

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

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 (see section 4.2). 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 4.3 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), anti-platelet agents such as low-dose acetylsalicylic acid as well as those ingesting excessive amount of alcohol 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.

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.

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 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 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.

Respiratory disorders

Feldene should be used with caution in patients with or a history of bronchial asthma (see section 4.3).

Poor Metabolisers 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).

Hepatic Effects

Piroxicam can cause fatal hepatitis and jaundice. Although such reactions are rare, if abnormal liver functions 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.

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 drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), 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). Evidence from observational studies suggests that piroxicam may be associated with a higher risk of serious skin reactions than other non-oxicam NSAIDs. Patients appear to be at highest risk of these reactions 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.

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.

Feldene should be used with caution in patients with renal, hepatic and cardiac impairment. In rare cases, non-steroidal anti-inflammatory drugs may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. Such agents inhibit the synthesis of the 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 with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, such patients should be carefully monitored whilst receiving NSAID 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.

The use of Feldene with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Impaired female fertility
The use of Feldene 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 Feldene should be considered.

Excipient information
Feldene Melt contains aspartame which is a source of phenylalanine. Phenylalanine may be harmful to patients with phenylketonuria (PKU).

4.5 Interaction with other medicinal products and other forms of interaction

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

Anticoagulants: NSAIDs, including piroxicam, may enhance the effects of anticoagulants, such as warfarin. Therefore the use of piroxicam with concomitant anticoagulant 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).

Aspirin and other Non-Steroidal Anti-Inflammatory Drugs: Feldene, like other non-steroidal anti-inflammatory drugs decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

As with other NSAIDs, the use of piroxicam together with acetylsalicylic acid or concomitant use with other NSAIDs, including other piroxicam formulations, must be avoided, since data are inadequate to show that 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 acetylsalicylic acid reduces the plasma piroxicam concentration to about 80% of the usual value.

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

Ciclosporin, Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs are given with ciclosporin or tacrolimus.

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.

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

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

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 the renal function compromised), 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, especially in elderly patients. 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.

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 when administering Feldene to patients on highly protein-bound drugs.

Lithium: Non-steroidal anti-inflammatory drugs, including Feldene, have been reported to increase steady state plasma lithium levels. It is recommended that these levels are monitored when initiating, adjusting and discontinuing Feldene.

Feldene, like other non-steroidal anti-inflammatory drugs, may interact with the following drugs / classes of therapeutic agents:

Antihypertensives: antagonism of the hypotensive effect

Quinolone antibiotics: possible increased risk of convulsions

Mifepristone: NSAIDs could interfere with mifepristone-mediated termination of pregnancy

Methotrexate: Reduced excretion of methotrexate, possibly leading to acute toxicity. 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.

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 safety of Feldene during pregnancy or during lactation has not yet been established. 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. In view of the known effects of NSAIDs on the foetal CV system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3).

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.

From the 20th week of pregnancy onward, Feldene 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, Feldene should not be given unless clearly necessary. If Feldene 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 Feldene for several days from gestational week 20 onward. Feldene 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);
- renal dysfunction (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, Feldene is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding
A study indicates that piroxicam appears in the 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	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)

System Organ Class	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, Leukopenia, Thrombocytopenia				Aplastic anaemia, Haemolytic anaemia
Immune system disorders					Anaphylaxis, Serum sickness
Metabolism and nutrition disorders	Anorexia, Hyperglycaemia	Hypoglycaemia			Fluid retention
Psychiatric disorders					Depression, Hallucinations, Mental confusion, Mood alterations, Insomnia, Nervousness, Dream abnormalities
Nervous system disorders	Headache, Dizziness, Somnolence, Vertigo				Paraesthesia
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	Epigastric distress, Nausea, Constipation, Abdominal discomfort, Flatulence, Abdominal pain, Diarrhoea, Vomiting, Indigestion	Stomatitis			Perforation, Ulceration, Pancreatitis, Gastrointestinal bleeding (including hematemesis and melena), Gastritis

System Organ Class	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)
Hepatobiliary disorders					Fatal hepatitis, Jaundice
Renal and urinary disorders			Renal failure, Nephrotic syndrome, Interstitial nephritis, Renal papillary necrosis		Glomerulonephritis
Skin and subcutaneous tissue disorders	Skin rash, Pruritis			Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4)	Angioedema, DRESS syndrome, Vesiculo bullous reactions, Dermatitis exfoliative, Erythema multiforme, Photoallergic reactions, Fixed drug eruption (see section 4.4), Non-thrombocytopenic purpura (Henoch-Schoenlein), Onycholysis, Alopecia, Urticaria
Reproductive system and breast disorders					Female fertility decreased
General disorders and administration site conditions	Oedema (mainly of the ankle)				Malaise
Investigations	Decreases in haemoglobin and haematocrit unassociated with obvious gastro-intestinal bleeding, Increased serum transaminase levels, Weight increase				Positive ANA (antinuclear antibody), Weight decrease

Gastrointestinal:
These are the most commonly encountered side-effects but in most instances do not interfere with the course of therapy. Objective evaluations of gastric mucosa appearances and intestinal blood loss show that 20mg/day of Feldene administered either in single or divided doses is significantly less irritating to the gastrointestinal tract than aspirin. Some epidemiological studies have suggested that piroxicam is associated with higher risk of gastrointestinal adverse reactions compared with some NSAIDs, but this has not been confirmed in all studies. Administration of doses exceeding 20mg daily (of more than several days duration) carries an increased risk of gastrointestinal side effects, but they may also occur with lower doses see Section 4.2).

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. The possibility of precipitating congestive heart 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).

Liver function:
Changes in various liver function parameters have been observed.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA yellow card in the Google Play or Apple App Store.

4.9 Overdose

In the event of acute overdosage with Feldene, supportive and symptomatic therapy is indicated. There are no specific antidotes. First line management of overdose should be the use of activated charcoal. Studies indicate that administration of activated charcoal may result in reduced re-absorption of piroxicam, thus reducing the total amount of active drug available.

Dependent upon amount ingested and time since ingestion, gastric lavage may need to be considered as a second-line option only by experienced clinicians and not for routine use.

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

Piroxicam is a non-steroidal anti-inflammatory agent which also possesses analgesic and antipyretic properties. Oedema, erythema, tissue proliferation, fever and pain can all be inhibited in laboratory animals by the administration of piroxicam. It is effective regardless of the aetiology of the inflammation. While its mode of action is not fully understood, independent studies *in vitro* as well as *in vivo* have shown that piroxicam interacts at several steps in the immune and inflammation responses through:

Inhibition of prostanoid synthesis, including prostaglandins, through a reversible inhibition of the cyclo-oxygenase enzyme.

Inhibition of neutrophil aggregation.

Inhibition of polymorphonuclear cell and monocyte migration to the area of inflammation.

Inhibition of lyosomal enzyme release from stimulated leucocytes.

Reduction of both systemic and synovial fluid rheumatoid factor production in patients with seropositive rheumatoid arthritis.

It is established that piroxicam does not act by pituitary-adrenal axis stimulation. In-vitro studies have not revealed any negative effects on cartilage metabolism.

5.2 Pharmacokinetic properties

Absorption

Piroxicam is well absorbed following oral or rectal administration. With food there is a slight delay in the rate but not the extent of absorption following administration. 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 1 year produces similar blood levels to those seen once steady state is first achieved.

Distribution

Drug plasma concentrations are proportional for 10 and 20mg doses and generally peak within 3 to 5 hours after medication. A single 20mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml while maximum plasma concentrations, after repeated daily ingestion of 20mg piroxicam, usually stabilise at 3 to 8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days.

Treatment with a loading dose regimen of 40mg daily for the first 2 days followed by 20mg daily thereafter allows a high percentage (approximately 76%) of steady state levels to be achieved immediately following the second dose. Steady state levels, area under the curves and elimination half-life are similar to that following a 20mg daily dose regimen.

Biotransformation

A multiple dose comparative study of the bioavailability of the injectable forms with the oral capsule has shown that after intramuscular administration of piroxicam, plasma levels are significantly higher than those obtained after ingestion of capsules during the 45 minutes following administration the first day, during 30 minutes the second day and 15 minutes the seventh day. Bioequivalence exists between the two dosage forms.

A multiple dose comparative study of the pharmacokinetics and the bioavailability of Feldene FDDF with the oral capsule has shown that after once daily administration for 14 days, the mean plasma piroxicam concentration time profiles for capsules and Feldene FDDF were nearly superimposable. There were no significant differences between the mean steady state C_{max} values, C_{min} values, T½, or T_{max} values. This study concluded that Feldene FDDF (Fast Dissolving Dosage Form) is bioequivalent to the capsule after once daily dosing. Single dose studies have demonstrated bioequivalence as well when the tablet is taken with or without water.

Elimination

Piroxicam 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.

6.1. List of excipients

Feldene Melt: Gelatin; Mannitol.; Aspartame (E951); Citric Acid. Purified Water

6.2 Incompatibilities

None stated.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Blister strip PVC/PVdC and paper foil laminate containing 10 units. Each pack contains 30 units (3 x strips of 10 tablets).

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
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Kent
CT13 9NJ

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/0352

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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