AUSTRALIAN PRODUCT INFORMATION – FELDENE® and FELDENE-D® (PIROXICAM)

1. NAME OF THE MEDICINE

Piroxicam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FELDENE (piroxicam) 10 mg and 20 mg capsules.

FELDENE-D (piroxicam) 20 mg tablets.

Excipient(s) with known effect

FELDENE 10 mg and 20 mg capsules contain lactose monohydrate.

FELDENE-D dispersible 20 mg tablets contain lactose monohydrate.

For the full list of excipients, see Section 6.1 - List of excipients.

3. PHARMACEUTICAL FORM

FELDENE 10 mg capsules are blue and maroon in colour, marked *FEL10* on one side and *Pfizer* on the other.

FELDENE 20 mg capsules are maroon in colour, marked *FEL20* on one side and *Pfizer* on the other.

FELDENE-D 20 mg dispersible tablets are white, scored, capsule-shaped and marked *FEL/20* on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piroxicam is indicated for symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

4.2 Dose and method of administration

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

After assessing the risk versus benefit for each patient, use the minimum effective dose for the shortest duration possible. The duration of treatment should preferably be limited to 14 days. If continued treatment is considered necessary, this should be accompanied by evaluation at 14 days and subsequent frequent review with regards to efficacy, risk factors and ongoing need for treatment.

The dose should be adjusted to each individual patient's response and toleration. In studies to date, the optimal response generally has been achieved at a daily dose of 20 mg, given as a single dose. The recommended starting dose is 10 mg and administration of doses higher than 20 mg daily carries an increased risk of adverse effects and is not recommended.

FELDENE-D dispersible tablets should be dispersed in a minimum of 50 mL of water and then swallowed.

4.3 Contraindications

Piroxicam should not be administered to patients with active peptic ulcerations, active gastrointestinal ulceration, bleeding or perforation, active inflammatory disease of the gastrointestinal tract or with a history of these conditions.

Piroxicam should not be used in those patients who have previously shown a hypersensitivity to the drug or in whom a hypersensitive reaction(s) (e.g. asthma, nasal polyps, angioedema or urticaria) has been precipitated by aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) since cross-sensitivity exists.

Piroxicam should not be administered to patients with a history of previous severe allergic drug reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or those who have exhibited a previous skin reaction (regardless of severity) to piroxicam.

Piroxicam is contraindicated in the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Piroxicam is contraindicated in patients with severe renal failure.

Piroxicam is contraindicated in patients with severe hepatic impairment.

Piroxicam is contraindicated in patients with severe heart failure.

Piroxicam should not be administered concomitantly with other NSAIDs, including cyclooxygenase-2 (COX-2) selective NSAIDs and aspirin at analgesic doses.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. 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. Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs. Piroxicam should only be commenced after careful weighing of the risks and benefits in each individual patient.

Cardiovascular Effects

Cardiovascular Thrombotic Events

NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with dose or

duration of use. 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 CV disease, history of atherosclerotic CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimise the potential risk for an adverse CV event in patients treated with piroxicam, especially those with CV risk factors, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur (See section 4.3 - Contraindications).

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV events associated with NSAID use.

Hypertension

NSAIDs, including piroxicam, may lead to the onset of new hypertension or worsening of pre-existing hypertension. Patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. For example, the anti-hypertensive effect of thiazide diuretics and beta-blocking agents is antagonised by NSAIDs. NSAIDs, including piroxicam, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and throughout the course of therapy.

Heart Failure

Fluid retention and oedema (mainly ankle oedema) has been reported in patients taking NSAIDs, including piroxicam. Therefore, piroxicam should be used with caution in patients with compromised cardiac function and other conditions predisposing to or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy

NSAIDs, including piroxicam, can cause serious, potentially fatal gastrointestinal (GI) toxicity, including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine.

GI toxicity can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. The frequency of such events may increase with dose or duration of use. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. 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 GI toxicity, relative to other NSAIDs (See section 4.3 - Contraindications).

Patients most at risk of developing these types of GI complications with NSAIDs are the elderly; patients with CV disease; patients using concomitant corticosteroids, antiplatelet drugs (such as aspirin), selective serotonin reuptake inhibitors (SSRIs), patients ingesting alcohol or patients with a history of GI disease (such as ulceration, GI bleeding or inflammatory conditions); and patients with a history of smoking or alcoholism. Piroxicam should either not be prescribed, or be prescribed with caution in these patients (See section 4.3 - Contraindications).

Age over 70 years is associated with high risk of complications. The administration to patients older than 80 years should be avoided. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as low-dose aspirin are at increased risk of serious GI complications.

Patients and physicians should remain alert 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 GI complication is suspected during treatment, piroxicam should be discontinued immediately and additional clinical evaluation and treatment should be considered.

Asthma

Piroxicam should be used with caution in patients with asthma because bronchial smooth muscle spasm may be aggravated by prostaglandin inhibition.

Haemorrhagic Tendencies

Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined and in patients undergoing surgery and in patients with haemorrhagic disorders. Dosage requirements of coumarin anticoagulants and other drugs that are highly protein bound should be closely and very regularly monitored when these are administered concomitantly with piroxicam. Such drugs include warfarin, hydantoins, sulphonamides and sulfonylureas. Bleeding has been reported rarely when piroxicam as well as other NSAIDs have been administered to patients on coumarin type anticoagulants (See section 4.5 - Interactions with other medicines and other forms of interactions).

Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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 given with caution. Oral anticoagulants include warfarin/coumarin-type anticoagulants and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (See section 4.5 - Interactions with other medicines and other forms of interactions).

Masking of Signs of Infection

As with other NSAIDs, the anti-inflammatory, antipyretic and analgesic effects of piroxicam may mask the signs of infection (pain, fever etc.).

Ophthalmological Monitoring

Adverse ophthalmological effects have been observed with NSAIDs; accordingly patients who develop visual disturbances during treatment with piroxicam should have an ophthalmological examination.

Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens - Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Evidence from observational studies suggests that piroxicam may be associated with a higher risk of severe cutaneous adverse 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash, mucosal lesion or any other sign of hypersensitivity.

Use in Hepatic Impairment

As with other NSAIDs, borderline elevations of liver function tests may occur in up to 15% of patients. A patient with symptoms or signs suggesting impaired hepatic function or in whom an abnormal liver function test has been reported should be evaluated for evidence of development of some severe hepatic dysfunction. These abnormalities may progress, remain essentially unchanged or be transient with continued therapy. The ALT (SGPT) is probably the most sensitive indicator of liver dysfunction. Meaningful (3 x upper limit of normal) elevations of ALT or AST (SGOT) occurred in controlled trials in less than 1% of patients.

Physician and patients should remain alert for the hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms) and the steps to take should these signs and/or symptoms occur. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with piroxicam. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs consistent with liver disease develop or if systemic manifestations occur (e.g. eosinophilia, rash etc.) piroxicam should be discontinued.

Use in Renal Impairment

As with other NSAIDs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other pathology. In rare cases, NSAIDs may cause interstitial nephritis, glomerulitis, haematuria, proteinuria, papillary necrosis and, occasionally, nephrotic syndrome.

NSAIDs 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 an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to the pretreatment state on discontinuation of the NSAID. Patients at greatest risk of this complication include those with impaired liver or renal function (e.g. liver cirrhosis, nephrotic syndrome, overt renal disease), with heart failure, taking diuretics or the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

Blood urea nitrogen elevation has been observed in some patients. These elevations are not progressive over the course of treatment with piroxicam, a plateau being reached which returns to or towards baseline levels if treatment is stopped. The rise in blood urea nitrogen as a rule is not associated with elevations in serum creatinine.

As with other NSAIDs, it is recommended that piroxicam be given under close supervision in patients with a history of impaired renal function and periodic renal function tests carried out.

Caution should be used when initiating treatment with piroxicam in patients with severe dehydration. Caution is also recommended in patients with kidney disease (See section 4.3 - Contraindications).

Lower doses should be considered in patients with impaired renal function and they should be carefully monitored.

Use in the Elderly

See Section 4.4 – Special warnings and precautions for use, Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy; Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics; and Use in Renal Impairment. See also Section 4.5 Interactions with other medicines and other forms of interactions, Anti-hypertensives.

Paediatric Use

The use of piroxicam in children under the age of 12 years is not recommended as safety and efficacy in this age group are not established.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Anticoagulants

The concurrent use of NSAIDs and coumarin anticoagulants (including warfarin) has been associated with severe, sometimes fatal, haemorrhage. Patients should be monitored closely if piroxicam is administered concurrently with oral anticoagulants, including warfarin/coumarin-type anticoagulants and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban) (See section 4.4 - Special warnings and precautions for use, Use with Oral Anticoagulants).

Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

The exact mechanism of the interaction between warfarin and NSAIDs is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs.

Warfarin should be used in combination with piroxicam only if necessary (See section 4.5 - Interactions with other medicines and other forms of interactions, Protein-Bound Agents).

Protein-bound Agents

Piroxicam is highly protein bound and therefore might be expected to displace other protein bound drugs. The physician should closely monitor dosage requirements of drugs that are highly protein bound when these are administered concomitantly with piroxicam. Such drugs include coumarin anticoagulants (e.g. warfarin), hydantoins, sulphonamides and sulphonylureas.

Methotrexate

When methotrexate is administered concurrently with NSAIDs, including piroxicam, the NSAID may decrease elimination of methotrexate resulting in increased plasma levels of methotrexate. Extreme care should be exercised in giving methotrexate, especially high doses, to patients on piroxicam therapy, because lethal interactions have been reported between NSAIDs and methotrexate.

Aspirin

As with other NSAIDs, the use of piroxicam in conjunction with aspirin or the concomitant use of two NSAIDs is not recommended because data are inadequate to demonstrate that the combination produces greater benefit than with the drug alone and the potential for adverse reactions is increased (See sections 4.3 - Contraindications and 4.4 - Special warnings and precautions for use).

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when piroxicam is administered in conjunction with aspirin (3900 mg/day) but concomitant administration of antacids has no effect on piroxicam plasma levels.

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

Lithium

NSAIDs including piroxicam have been shown to decrease the renal clearance and increase steady state plasma concentrations of lithium. Plasma lithium concentrations should be monitored when initiating, adjusting or discontinuing concurrent piroxicam therapy.

Cimetidine

Results of two separate studies indicate a slight increase in absorption of piroxicam following cimetidine administration but no significant changes in elimination parameters. Cimetidine increases the area under the curve (AUC 0-120 hours) and C_{max} of piroxicam by approximately 13 to 15%. Elimination rate constants and half-life show no significant differences. The small but significant increase in absorption is unlikely to be clinically significant.

Cholestyramine

Cholestyramine has been shown to enhance the oral clearance and decrease the half-life of piroxicam. To minimise this interaction, it is prudent to administer piroxicam at least 2 hours before or 6 hours after cholestyramine.

Frusemide

As with other NSAIDs, care should be taken in the administration of piroxicam in combination with frusemide for treating cardiac failure because NSAIDs antagonise the diuretic effect of frusemide.

Anti-hypertensives

NSAIDs can reduce the efficacy of diuretics and other anti-hypertensive drugs, including ACE inhibitors, angiotensin II antagonists (AIIAs; also known as angiotensin receptor blockers or ARBs) and beta-blockers (See section 4.4 - Special warnings and precautions for use, Hypertension).

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 a diuretic with a cyclo-oxygenase inhibitor can increase the deterioration of 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 a diuretic. Thus, caution should be taken when administrating piroxicam with these drugs, especially in elderly patients (See section 4.4 - Special warnings and precautions for use, Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics).

Patients should be adequately hydrated and the need to monitor renal function should be assessed before, and periodically during, concomitant treatment.

Cardiac Glycosides (Digoxin and Digitoxin)

Concomitant administration of NSAIDs with cardiac glycosides (e.g. digoxin, digitoxin) may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.

Corticosteroids or Selective Serotonin Reuptake Inhibitors (SSRIs)

Concomitant administration of NSAIDs and corticosteroids or selective serotonin reuptake inhibitors (SSRIs) increases the risk of gastrointestinal ulceration or bleeding.

Ciclosporin or Tacrolimus

Concomitant administration of NSAIDs with ciclosporin or tacrolimus increases the risk of nephrotoxicity.

Poor Metabolisers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolisers 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.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Based on the mechanism of action, the use of NSAIDs, including piroxicam, 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 piroxicam, should be considered.

Use in Pregnancy – Category C

Inhibition of prostaglandin synthesis might adversely affect pregnancy. 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.

NSAIDs given during the latter part of pregnancy, may cause premature closure of the fetal ductus arteriosus, prolong labour and delay birth. Therefore, piroxicam should be avoided during the third trimester of pregnancy. Continuous treatment with NSAIDs during the last month of pregnancy should be given only on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal 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 is usually reversible. Pregnant women on piroxicam should be closely monitored for amniotic fluid volume.

Although no teratogenic effects were seen in animal testing, piroxicam should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh the potential risk.

Use in Lactation

Studies in 6 women treated for up to 52 days have shown that piroxicam appeared in breast milk in a concentration approximately 1% to 3% of that reached in maternal plasma.

Piroxicam is not recommended for nursing mothers unless the expected benefits outweigh any potential risk, as clinical safety has not been demonstrated.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Results from clinical trials involving approximately 2300 patients (of whom about 400 were treated for more than one year and 170 for more than two years) indicate that about 30% of patients reported side effects at a dose of 20 mg/day. This increased with doses of 30-40 mg/day.

More Common Reactions (more than 3%)

Gastrointestinal: These have been the most frequent side effects, occurring in about 20%. Approximately 5% discontinued therapy, with an overall incidence of peptic ulcer of about 1%. The gastrointestinal side effects included abdominal discomfort (5.7%), flatulence (5.2%), nausea (4.8%), abdominal pain (4.7%), epigastric distress (4.1%), constipation (3.8%) and diarrhoea (3.2%).

Central Nervous System: Dizziness (4.1%), headache (4.1%).

Less Common Reactions (less than 3%)

Auditory and Vestibular: Tinnitus, vertigo, deafness.

Laboratory Abnormalities: Elevated levels of liver enzymes (LDH, alkaline phosphatase, transaminases); elevation of blood urea nitrogen (BUN) and serum creatinine; depression of levels of haemoglobin and haematocrit; depression of levels of serum proteins, platelet and white blood cell count.

Cardiovascular: Hypertension, tachycardia, palpitations.

Dermatological: Skin rash (2.4%), pruritus (1.1%), onycholysis, alopecia. Photo-allergic reactions have been infrequently associated with therapy. As with other NSAIDs, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), toxic epidermal necrolysis (Lyell's disease) and Stevens-Johnson syndrome may develop in rare cases. Vesiculobullous reactions have been reported rarely.

Gastrointestinal: Anorexia, vomiting, indigestion, pancreatitis, hepatitis.

Central Nervous System: Sedation, drowsiness (2.1%), others (each less than 1%) include amnesia, anxiety, depression, malaise, hallucinations, insomnia, dream abnormalities, nervousness, paraesthesia, personality change, tremors, akathisia.

Genito-urinary: Oedema (2.7%), others (less than 1%) dysuria, urinary frequency, haematuria, oliguria, menorrhagia.

Eyes, Nose, Throat: Stomatitis (1.0%), blurred vision, eye irritation/ swelling, epistaxis, glossitis.

Haematological: Decreases in haemoglobin and haematocrit, unassociated with obvious gastrointestinal bleeding, have occurred. Anaemia has been reported. Thrombocytopenic and non-thrombocytopenic purpura (Henoch-Schonlein), petechial rash, ecchymosis, leucopenia and eosinophilia have been reported. Rare cases of aplastic anaemia and haemolytic anaemia are also reported.

Miscellaneous (each less than 1.0%): Breathlessness, chest pain, hyperglycaemia, hypoglycaemia, thirst, chills, sweating, flushing, increased appetite, weight increase or decrease. Rare anecdotal reports of positive antinuclear antibodies.

Serious or Life Threatening Reactions: Peptic ulceration and gastrointestinal haemorrhage may occur. The patient should be admitted to hospital to determine the underlying lesion, followed by appropriate treatment.

Post-marketing Experience

Additional adverse events reported post-marketing include:

Central Nervous System: Aseptic meningitis.

Dermatological: Dermatitis exfoliative, erythema multiforme.

Renal: Nephrotic syndrome, glomerulonephritis, interstitial nephritis; renal failure.

Body as a Whole: Fluid retention.

Gynaecological: Decreased female fertility.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Insufficient human data are available to fully assess the toxicity following acute overdosage.

Signs and Symptoms

Mild symptoms of lethargy, drowsiness and gastrointestinal upset have been reported. Rarely severe overdose may cause hypotension, coma, respiratory depression, gastrointestinal bleeding or acute renal insufficiency. Low grade fever and sinus tachycardia have been reported following NSAID overdose. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Recommended Treatment

In the event of overdosage with piroxicam 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. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or who have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected. Haemodialysis, forced diuresis, or haemoperfusion are probably ineffective in enhancing elimination, since the drug is highly protein-bound. There appears to be no indication for alkalinisation of the urine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Piroxicam is a NSAID which also possesses analgesic and antipyretic properties. 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 the following mechanisms:

- Inhibition of prostanoid synthesis including prostaglandins, through a reversible inhibition of the cyclooxygenase enzyme.
- Inhibition of neutrophil aggregation in blood vessels.
- Inhibition of lysosomal enzyme release from stimulated leucocytes.
- Inhibition of polymorphonuclear cell and monocyte migration to the area of inflammation.
- Inhibition of superoxide anion generation by the neutrophil.
- Reduction of both systemic and synovial fluid rheumatoid factor production in patients with seropositive rheumatoid arthritis.

Piroxicam has been shown to inhibit chemotaxis of polymorphonuclear leucocytes and the migration of leucocytes in canine synovitis test. The drug also inhibits collagen-induced platelet aggregation. It is established that piroxicam does not act by pituitary-adrenal axis stimulation. Studies *in vitro* have not revealed any negative effect on cartilage metabolism.

Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys. The pathology most often seen was that characteristically associated with the animal toxicology of NSAIDs: renal papillary necrosis and gastrointestinal lesions.

Clinical Trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Piroxicam is well absorbed following oral administration. The extent and rate of absorption are not influenced by administration in the fasting state. The plasma half-life is approximately 36-45 hours in man and stable plasma concentrations are maintained throughout the day on once daily dosage. After repeated administration, plasma concentrations increase for five to seven days, by which time a steady state is reached which is not exceeded following further constant daily drug administration.

Distribution

Piroxicam is highly protein bound (99%) and therefore might be expected to displace other protein bound drugs (See section 4.5 - Interactions with other medicines and other forms of interactions, Protein-Bound Agents).

Metabolism and Excretion

Piroxicam is extensively metabolised and less than 5% of the daily dose is excreted unchanged in urine and faeces. One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side chain followed by conjugation with glucuronic acid and urinary elimination. Approximately 5% of the dose is metabolised to and excreted as saccharin.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

FELDENE capsules contain the following inert ingredients:

- Lactose monohydrate,
- Maize starch,
- Magnesium stearate/sodium lauryl sulfate 9:1 blend,
- Gelatine,
- Erythrosine,
- Titanium dioxide,
- Brilliant blue FCF (10 mg capsule only),
- Indigo carmine (20 mg capsule only).

FELDENE-D dispersible tablets contain the following inert ingredients:

- Lactose monohydrate,
- Microcrystalline cellulose,
- Hyprolose,
- Sodium stearyl fumarate.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

FELDENE 10 mg capsules are available in PVC/Al blister packs of 50 capsules.

FELDENE 20 mg capsules are available in PVC/Al blister packs of 25 capsules.

FELDENE-D 20 mg dispersible tablets are available in PVC/Al blister packs of 25 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

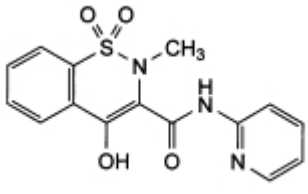
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

FELDENE and FELDENE-D contain the active ingredient piroxicam. Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) of the chemical class N-heterocyclic carboxamides of 1,2-benzothiazine-1,1-dioxide.

Piroxicam is an amphoteric compound. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.5) as determined by ultraviolet absorption spectrophotometry in methanol-water (2.5/97.5, v/v) solvent medium. It occurs as a white to off-white crystalline solid, poorly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It is a hygroscopic solid, which melts in the range 196 to 200°C.

Chemical Structure



Chemical name:	4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide
Molecular formula:	$C_{15}H_{13}N_3O_4S$
Molecular weight:	331.4

CAS Number

36322-90-4.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

FELDENE Capsules 10 mg and 20 mg: 24 January 1994.

FELDENE-D Tablets 20 mg: 24 November 1992.

10. DATE OF REVISION

8 April 2020

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
4.3	Define NSAIDs.
4.4	Correction of typographical error from "artherosclerotic" to "atherosclerotic". Correction of typographical error from "pruritis" to "pruritus".
4.4 and 4.8	Addition of DRESS Syndrome.
4.5	Alignment of cyclosporin to AAN (ciclosporin).