PRODUCT INFORMATION

FELDENE GEL®
(piroxicam)

NAME OF THE MEDICINE

Feldene Gel contains the active component piroxicam (anhydrous), a nonsteroidal anti-inflammatory agent of the chemical class N-heterocyclic carboxamides of 1, 2-benzothiazine-I, I-dioxide.

*Empirical formula: $\text{C}_{15}\text{H}_{13}\text{N}_{3}\text{O}_{4}\text{S}$

*Molecular weight: 331.4

CAS Number: 36322-90-4

*The structural formula of piroxicam is shown below.

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DESCRIPTION

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 (25197.5, 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.

FELDENE Gel is available in tubes as a clear pale yellow gel containing 0.5% anhydrous piroxicam (by weight) in a base made up of the following inactive ingredients:

Carbomer*980; propylene glycol; ethanol; benzyl alcohol; di-isopropanolamine; hydroxyethylcellulose; and purified water.
PHARMACOLOGY

*Mechanism of Action*

Piroxicam is a nonsteroidal anti-inflammatory agent 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 leukocytes.
- 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.

*Pharmacokinetics*

Pharmacokinetic and tissue distribution studies in rats and dogs have shown that piroxicam 0.5% gel is continuously and gradually released from the skin to underlying muscle or synovial fluid. In addition, equilibrium between skin and muscle or synovial fluid appears to be reached rapidly, within a few hours after application.

In human pharmacokinetic studies when a dose of 15 mg of piroxicam as FELDENE 0.5% Gel was applied topically to intact skin of the backs of 8 normal volunteers and any residue removed after 8 hours, serum concentrations rose steadily to a mean of 147 pg/L 23 hours after application, a peak level about 1/15 that following an equivalent oral dose. The elimination half-life was about 50 hours and most drug was recovered as the inactive 5-hydroxy metabolite. Furthermore, following repeated topical applications of FELDENE 0.5% Gel (20 mg piroxicam/day) to 20 normal volunteers for 14 consecutive days, it was estimated that the quantity of piroxicam bioavailable by the transdermal route represented 3% of oral bioavailability at equivalent dosage. Use of an occlusive dressing appeared to increase the bioavailability.
INDICATIONS

FELDENE 0.5% Gel is indicated for the temporary (up to two weeks) topical treatment of acute soft tissue-injuries including sprains, strains and tendonitis.

*CONTRAINDICATIONS

FELDENE Gel should not be used in those patients who have previously shown a hypersensitivity to the gel or piroxicam in any of its dosage forms or in whom a hypersensitive reaction(s) (e.g. asthma, rhinitis, nasal polyps, angioedema or urticaria) has been precipitated by aspirin or other nonsteroidal anti-inflammatory agents since cross-sensitivity exists.

*PRECAUTIONS

In common with other topical NSAIDs, the systemic absorption of FELDENE Gel is very low and systemic reactions occur infrequently. They have included minor gastrointestinal side effects such as nausea and dyspepsia. Cases of abdominal pain and gastritis have been reported rarely. There have been isolated reports of bronchospasm and dyspnoea.

FELDENE Gel should be used with extreme caution in patients with a peptic ulcer, active gastrointestinal bleeding or active inflammatory disease of the gastrointestinal tract or with a recent history of these conditions or severe renal impairment.

If local irritation develops, the use of FELDENE Gel should be discontinued and appropriate therapy instituted as necessary. Do not apply to the eyes or other mucosal surfaces. Do not apply FELDENE Gel to broken skin, infected sites, exudative dermatoses or other open skin lesions, or skin conditions affecting the site of application.

* Preclinical Safety Data

Acute and chronic toxicity and irritation studies have been carried out in animals. In an acute study, albino rats were given a single dermal application of gel of 5 g/kg. No deaths, toxic signs or skin irritation were observed and no gross changes were found at autopsy.

In a one month study, albino rats received a daily application of gel to dorsal skin of 1 g per rat. No skin irritation was noted at the treatment sites, and no drug-related changes were observed. The gel was also evaluated for primary skin irritation, eye irritation, and phototoxicity in rabbits and for photoallergy and skin sensitization potential in guinea pigs, all according to standard established protocols. No skin reactions were found after application of 0.5% gel or the vehicle to intact rabbit skin, however piroxicam gel produced slight erythema and oedema on abraded skin.

The anti-inflammatory and analgesic effects of FELDENE 0.5% Gel were studied in rats and guinea pigs using such standard models of pain and inflammation as carrageenan
induced rat paw oedema, ultraviolet erythema in guinea pigs, traumatic oedema in rats, cotton pellet induced granuloma formation in rats and adjuvant induced arthritis in cats. FELDENE 0.5% Gel was comparable to indomethacin 1% gel in all of these models and was comparable to orally administered piroxicam in inhibiting inflammation of the rat paw oedema model.

Oedema, erythema, tissue proliferation, fever and pain can all be inhibited in laboratory animals by the administration of FELDENE Gel.

* Interactions with Other Medicines

The following discussion describes the potential for systemically administered piroxicam to interact with other medications. Interactions between FELDENE Gel and other drugs have not been specifically studied.

The concurrent use of nonsteroidal anti-inflammatory agents and coumarin anticoagulants (including warfarin) has been associated with severe, sometimes fatal, haemorrhage. 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. These effects should be considered and patients monitored closely when anticoagulants are being used. Warfarin should be used in combination with FELDENE only if necessary.

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

Extreme care should also be exercised in giving methotrexate to patients using FELDENE Gel, because lethal interactions have been reported between nonsteroidal anti-inflammatory agents and methotrexate.

As with other NSAIDs, the use of FELDENE Gel 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.

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

Nonsteroidal anti-inflammatory agents 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 FELDENE Gel therapy.
Cimetidine: Results of two separate studies indicate a slight increase in absorption of orally administered piroxicam following cimetidine administration but no significant changes in elimination parameters. Cimetidine increases the area under the curve (AUC 0-120 hours) and $C_{\text{max}}$ 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. It is not known what effect the concurrent administration of cimetidine has on the pharmacokinetics of topically administered piroxicam.

As with other nonsteroidal anti-inflammatory agents, care should be taken in the administration of FELDENE Gel in combination with frusemide for treating cardiac failure because nonsteroidal anti-inflammatory agents antagonize the diuretic effect of frusemide.

**Use During Pregnancy - CATEGORY C.**

Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, prolong labour and delay birth. Continuous treatment with nonsteroidal anti-inflammatory drugs 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.

Although no teratogenic effects were seen in animal testing, FELDENE Gel 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.

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

**Use in Children**

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

**ADVERSE REACTIONS**

Side effects possibly related to treatment with FELDENE Gel have been reported infrequently. In clinical trials the vast majority of side effects involved mild or moderate local irritation, erythema, rash, pityroid desquamation, pruritus, and related local reactions at the application site. Mild but transient skin discolouration and staining of clothing have been noted when the gel is not rubbed in completely.
In post-marketing experience, the following additional dermatological effects have been reported: contact dermatitis, eczema and photosensitivity skin reaction.

The systemic absorption of FELDENE Gel is very low. In common with other topical NSAIDs, systemic reactions occur infrequently and have included minor gastrointestinal side effects such as nausea and dyspepsia. Cases of abdominal pain and gastritis have been reported rarely. There have been isolated reports of bronchospasm and dyspnoea.

Photo-allergic reactions have been infrequently associated with systemic administration of FELDENE.

**DOSAGE AND ADMINISTRATION**

FELDENE Gel at a dosage of one gram, approximately 3 cm linear (corresponding to 5 mg of piroxicam), should be applied to the affected site three or four times per day for up to two weeks. FELDENE Gel is intended for external use only. No occlusive dressing should be employed. Rub in the gel leaving no residual material on the skin.

**OVERDOSE**

Insufficient human data are available to fully assess the toxicity following acute overdosage. Mild symptoms of lethargy, drowsiness and gastrointestinal upset have been reported following acute overdosage with systemically administered piroxicam. 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.

In the event of overdosage (eg accidental ingestion) with FELDENE Gel, 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 alkalisation of the urine.

In the case of accidental ingestion, seek professional advice or contact the Poisons Information Centre (Australia 13 11 26*) for advice on the management of an overdose. Do this even if there are no signs of discomfort or poisoning.

**PRESENTATION AND STORAGE CONDITIONS**

Gel: 5 mg/g in 25 g and 50 g tubes.

Store below 30°C.
*POISON SCHEDULE

Unscheduled

*NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
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*DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 17 April 2000

Date of Most Recent Amendment: 31 March 2009

* Please note changes in Product Information.