PRODUCT MONOGRAPH

FROBEN
Tablets 50 and 100 mg
B.P.

FROBEN SR
200 mg sustained release capsules
(flurbiprofen)

Non-steroidal anti-inflammatory agent

Abbott Laboratories, Limited
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Control # 071577

NAME OF DRUG

FROBEN

Tablets 50 and 100mg

B.P.

FROBEN SR

200 mg sustained release capsules

(flurbiprofen)

THERAPEUTIC CLASSIFICATION

Non-steroidal anti-inflammatory agent

ACTIONS AND CLINICAL PHARMACOLOGY

Froben (flurbiprofen) is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic activity. Although its mechanism of action has not been completely elucidated it has been shown to be an inhibitor of prostaglandin synthesis, specifically cyclo-oxygenase, and to some extent lipoxygenase, and is not due to pituitary-adrenal stimulation.

Froben is well absorbed and the rate of absorption is not altered with old age. Following a single oral dose of 100 mg, peak plasma levels are achieved in about 2 hours. Absorption may be delayed in some individuals when administered with food but the total amount of drug absorbed is not affected. The elimination half-life is approximately 4 hours. When the drug is administered daily, steady state concentrations are reached with no drug accumulation. Twenty to 25% of flurbiprofen is recovered from the urine as free and conjugated unchanged drug, with 60 to 80% being hydroxylated metabolites. At therapeutic blood levels, flurbiprofen is at least 99% bound to serum proteins. Excretion of Froben is completed 24 hours after the final dose.

Bioavailability for Froben SR is comparable to that of standard Froben with no evidence of dose dumping or excessive accumulation. Steady state is reached within 2 to 3 days. Froben SR is less rapidly absorbed than the conventional Froben tablet, reaching maximum plasma concentrations in a longer period of time (see also under PHARMACOKINETICS).

INDICATIONS

For the symptomatic treatment of rheumatoid arthritis, osteo-arthritis and ankylosing spondylitis.

Froben (flurbiprofen) is also indicated for the relief of pain associated with dysmenorrhea.

CONTRAINDICATIONS

1. Peptic ulcer or active inflammatory disease of the gastrointestinal system.
2. Known or suspected hypersensitivity to Froben (flurbiprofen). Froben should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

- Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's) including Froben.

- Froben should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

-Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

- Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Use in Pregnancy and Lactation

- Froben (flurbiprofen) should not be used during pregnancy, or nursing mothers as its safety

under

these conditions has not been established. Although no teratogenic effects were seen in animal studies, parturition was delayed and prolonged and the number of stillbirths was increased. Froben has been found to cross the placental barrier, but it is not known if it is secreted in breast milk.

Use in Children

- The safety and efficacy of Froben has not been established in children, and therefore its use in this age group is not recommended.

PRECAUTIONS

General precautions:

Elderly patients, particularly women, should be carefully followed for the appearance of side effects and the dosage decreased accordingly.

Gastro-intestinal system:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs Froben (flurbiprofen) should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastro-intestinal side effects or allow continuation of Froben therapy when and if these adverse reactions appear.

Renal function:

As with other nonsteroidal anti-inflammatory drugs, long-term administration of Froben to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in

prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Froben (flurbiprofen) and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of Froben should be anticipated and patients carefully monitored. During long-term therapy kidney function should be monitored periodically.

Hepatic function:

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued. During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with Froben. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. Froben should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.
Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when Froben is administered.

Blood dyscrasias associated with the use of non-steroidal anti-inflammatory drugs are rare, but could be with severe consequences.

Infection:

In common with other anti-inflammatory drugs, Froben (flurbiprofen) may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of Froben and other non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

DRUG INTERACTIONS

Acetylsalicylic acid (ASA) or other NSAID's:

The concomitant administration of ASA with flurbiprofen caused decreased serum levels and peak concentrations of flurbiprofen. The rates of absorption and elimination of flurbiprofen were not affected.

Digoxin:

Flurbiprofen does not change the rate of elimination of digoxin and the rate of elimination of flurbiprofen is not altered by co-administration of digoxin. Although, digoxin absorption may be delayed during co-administration of flurbiprofen.

Coumarin Type Anti-Coagulants

In a short term study Froben did not significantly affect prothrombin time but the bleeding time increased slightly, although it remained within the normal range. Froben should therefore be administered with caution to patients on concomitant coumarin-type anticoagulant therapy. Such patients should be closely monitored.

Oral Hypoglycaemic Drugs:

Co-administration of flurbiprofen with glibenclamide, metformin, chlorpropamide or

phenformin did not lead to interaction effects of any clinical significance. A tendency towards a reduction in blood sugar levels occurred over a 24 hour period however no hypoglycaemic reactions occurred. No interaction in terms of blood sugar or immuno-reactive insulin occurred following the co-

administration of flurbiprofen and tolbutamide.

Methotrexate:

Caution is advised in the concomitant administration of flurbiprofen and methotrexate since non-steroidal anti-inflammatory agents have been reported to increase the blood concentration of methotrexate, thereby possibly enhancing its toxicity.

Lithium:

Non-steroidal anti-inflammatory agents have been reported to increase the steady state plasma levels of lithium. It is recommended that lithium plasma levels be monitored when co-administering it with flurbiprofen.

Diuretics:

Froben antagonizes the action of IV or oral furosemide.

Anti-hypertensives:

No significant alterations in the pharmacokinetics of either propranolol or atenolol followed pre-treatment with placebo or flurbiprofen. However, pre-treatment with flurbiprofen attenuated the effects of propranolol on blood pressure but not on heart rate. The hypotensive effect caused by atenolol was attenuated to a lesser degree following flurbiprofen pre-treatment.

Antacids:

The pharmacokinetics of a single oral dose of flurbiprofen are not altered by the concomitant administration of a magnesium and aluminium hydroxide antacid formulation.

Clinical Laboratory Tests:

Flurbiprofen and Thyroid Function Tests:

Flurbiprofen does not modify the laboratory parameters of thyroid function.

Froben is extensively bound to plasma protein and thus patients receiving concomitant drugs such as oral diabetic agents, sulfonamides, anti-coagulants, and phenytoin should be

monitored closely for side effects and/or clinical effectiveness and dosage adjustments made, if necessary.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

FROBEN TABLETS

The adverse reaction incidences were those reported during controlled clinical trials and include data from 2,141 patients on the conventional Froben tablets. Gastrointestinal adverse reactions were the most common, with ulceration and bleeding the most severe. The trials included 55 patients who received flurbiprofen for 3 months, 85 for 6 months at doses up to 300 mg daily, and 191 who received it for 3 years at a dose of 200 mg daily. The adverse report figures below represent the percent of treated patients reporting an adverse reaction.

Gastrointestinal (26.4%)

Dyspepsia (5.9%); nausea (with or without vomiting) (5.4%); gastrointestinal pain (4.5%); gastrointestinal bleeding (0.3%); diarrhea (2.3%); constipation (1.6%); gastritis (0.3%); flatulence (0.3%); anorexia (0.5%); peptic ulceration (0.3%); melena (0.1%); stomatitis (0.3%); others (4.7%). Although not reported in this series of clinical trials, glossitis and eructation have been observed.

Central Nervous System (7.2%)

Headache (2.0%); dizziness (1.6%); depression (0.6%); drowsiness (0.4%); insomnia (0.2%); confusion (0.2%); other (2.2%). Although not reported in this series of clinical trials, vertigo, paraesthesia, nervousness, mood alteration, ataxia, and tremor have been observed.

Dermatological (1.8%)

Rash (0.9%); pruritus (0.6%); urticaria (0.1%); and dryness of skin (0.1%). Two cases of Stevens-Johnson syndrome have been reported.

Renal (0.9%)

Edema (0.6%); frequency (0.3%); and hematuria (0.1%). Although not reported in this series of trials, dysuria, urinary incontinence, and urine abnormalities (decreased osmolality, albuminuria) have been reported.

Hematological (0.3%)

Epistaxis (0.2%) and anemia (0.1%). Although not seen in this series of clinical trials, aplastic anemia, thrombocytopenia, granulocytopenia, leukopenia, purpura, and petechia have been observed.

Respiratory (1.2%)

Dry mouth/nose (0.4%); chest pain (0.3%); and dyspnea (0.1%). Although not seen in this series of clinical trials, asthma has been observed.

Cardiovascular (0.3%)

Cramps (0.1%) and palpitations (0.1%).

Miscellaneous (3.6%)

Weight gain/loss (0.2%); exhaustion (0.6%); sweating (0.4%); hot flushes (0.3%); and others (2.1%). Although not seen in this series of clinical trials, vaginal hemorrhage has been reported.

Hepatic

Although not reported in this series of clinical trials, increased SGOT and alkaline phosphatase and hepatitis have been reported.

Special Senses

One case of tinnitus was reported. Although not seen in this series of studies, blurred vision, conjunctivitis, photophobia, abnormal accommodation, corneal opacity and taste alteration have been reported.

FROBEN SR

Reports from clinical trials involving a total of 2,231 patients on both the conventional tablets and the sustained release capsules (1,787 patients were administered the sustained released capsules) showed similar adverse reactions for both dosage forms.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No fatal cases of overdosage have been reported in conjunction with Froben (flurbiprofen) ingestion and those suffering with overdosage recovered without sequelae. No specific

antidote is known. Stomach emptying is advisable and supportive and symptomatic treatment with maintenance of electrolytes and acid balance is recommended.

DOSAGE & ADMINISTRATION

ADULTS:

FROBEN TABLETS

Rheumatoid Arthritis:

The usual recommended initial dose is 150 to 200 mg per day given in 3 or 4 divided doses. Some patients may initially require 250 to 300 mg per day. The dose should be adjusted until the minimum effective maintenance dose is established. During the course of treatment, the maximum daily dose of 300 mg should be used only during symptom exacerbations and not for maintenance therapy.

Osteoarthritis:

The usual recommended initial dose is 100 to 150 mg per day given in 2 or 3 divided doses. Some patients may initially require 200 to 300 mg per day. The dose should be adjusted until the minimum effective maintenance dose is established. During the course of treatment, the maximum daily dose of 300 mg should be used only during symptom exacerbations and not for maintenance therapy.

Ankylosing Spondylitis:

The usual recommended initial dose is 200 mg per day given in 4 divided doses. Some patients may initially require 250 to 300 mg per day. The dose should be adjusted until the minimum effective maintenance dose is established. During the course of treatment the maximum daily dose of 300 mg should be used only during symptom exacerbations and not for maintenance therapy.

Dysmenorrhea:

The usual recommended dosage is 50 mg given four times daily, beginning with the onset of dysmenorrhea and ending with the cessation of pain.

FROBEN SR

This dosage form is recommended for maintenance therapy of patients whose dose has been previously adjusted to 200mg daily. The recommended daily dose of Froben SR is one 200 mg capsule, taken in the evening after food. The capsule should be swallowed whole.

CHILDREN:

The safety and efficacy of Froben has not been established in children and therefore its use in this group is not recommended.

AVAILABILITY

FROBEN TABLETS

Froben (flurbiprofen) is available as white, sugar coated tablets containing either 50 mg (overprinted "F50" in black) or 100 mg (overprinted "F100" in black) of flurbiprofen. Both the 50 mg and 100 mg tablets are presented in bottles of 100 and 1,000 tablets.

FROBEN SR CAPSULES

Froben SR (flurbiprofen) is available as a hard gelatin capsule with a yellow opaque cap and a transparent yellow body containing white to off-white beads, printed 'FSR' in black. Each capsule contains 200 mg flurbiprofen in sustained release form.

INFORMATION TO THE PATIENT

Froben (flurbiprofen) which has been prescribed to you by your doctor, is one of a large group of non-steroidal anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis, ankylosing spondylitis and for the relief of pain associated with dysmenorrhea. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

HOW TO TAKE YOUR MEDICATION

You should take Froben only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

Be sure to take Froben regularly as prescribed. In some types of arthritis, up to two weeks

may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

Dosage & Administration
ADULTS:
FROBEN TABLETS

Rheumatoid Arthritis:
The usual recommended initial dose is 150 to 200 mg per day given in 3 or 4 divided doses. Some patients may initially require 250 to 300 mg per day. The dose may be adjusted by your doctor until the minimum effective maintenance dose is established. During the course of treatment, your doctor may increase the daily dose to a maximum of 300 mg as a temporary measure to treat severe symptoms.

Osteoarthritis:
The usual recommended initial dose is 100 to 150 mg per day given in 2 or 3 divided doses. Some patients may initially require 200 to 300 mg per day. The dose may be adjusted by your doctor until the minimum effective maintenance dose is established. During the course of treatment, your doctor may increase the daily dose to a maximum of 300 mg as a temporary measure to treat severe symptoms.

Ankylosing Spondylitis:
The usual recommended initial dose is 200 mg per day given in 4 divided doses. Some patients may initially require 250 to 300 mg per day. The dose may be adjusted by your doctor until the minimum effective maintenance dose is established. During the course of treatment, your doctor may increase the daily dose to a maximum of 300 mg as a temporary measure to treat severe symptoms .

Dysmenorrhea:
The usual recommended dosage is 50 mg given four times daily, beginning with the onset

of dysmenorrhea and ending with the cessation of pain.

FROBEN SR

The recommended daily dose of Froben SR is one 200 mg capsule, taken in the evening after food. The capsule should be swallowed whole.

If you have not taken your dose of Froben SR at the prescribed time you may take it right away, but you should wait at least 12 hours before taking the next dose. You may then continue taking your dose at the prescribed time thereafter. NEVER DOUBLE DOSES.

IMPORTANT

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking Froben unless directed to do so by your physician. If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

Along with its beneficial effects, Froben like other NSAID drugs, may cause some undesirable reactions. Elderly frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

-bloody or black tarry stool;
-shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
-skin rash, swelling, hives or itching;
-indigestion, nausea, vomiting, stomach pain or diarrhea;
-yellow discoloration of the skin or eyes, with or without fatigue;
-any changes in the amount or color of your urine (such as dark; red or brown);
-swelling of the feet or lower legs;
-blurred vision or any visual disturbance;
-mental confusion, depression, dizziness, lightheadedness;
hearing problems.

ALWAYS REMEMBER

-Before taking this medication tell your doctor and pharmacist if you:

-are allergic to Froben or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflusinal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;

-have a history of stomach upset, ulcers, or liver or kidney diseases;

-are pregnant or intend to become pregnant while taking this medication;

-are breast feeding;

-are taking any medication (either prescription or non-prescription);

-have any other medical problem(s).

-While taking this medication:

-tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;

-be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this
medication;

-check with your doctor if you are not getting any relief or if any problems develop.

-report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.

-your regular medical checkups are essential.

-if you require more information on this drug, consult your doctor or pharmacist.

CHILDREN:

The safety and efficacy of Froben has not been established in children and therefore its use in this group is not recommended.

CHEMISTRY

Structural Formula and Chemistry

Flurbiprofen is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs.

Chemical (USAN) Name: 2-(2-fluoro-4-biphenylyl) propionic acid.

Molecular Formula: $C_{15}H_{13}0_2F$

Molecular Weight: 244

Description:
Flurbiprofen is a white to cream coloured powder which is sparingly soluble in water at acid pH but readily soluble above pH 7. It is relatively soluble in most organic solvents. Flurbiprofen exists as a racemic mixture of its two optical isomers.

Composition:
Froben tablets: flurbiprofen, carnauba wax, colloidal silicon dioxide, corn starch, dimethylpolysiloxane, gum juniper, iron oxide black, lactose, liquid glucose, magnesium stearate, povidone, shellac, sodium benzoate, soya lecithin, stearic acid, sucrose, talc and titanium dioxide.
Froben SR capsules: flurbiprofen, microcrystalline cellulose , Eudragit RS 100, magnesium stearate, polyethylene glycol 6000 and colloidal silicon dioxide.

Stability and Storage Recommendations:
Froben tablets: Store in a dry place at 15 - 25°C.
Froben SR capsules: Store in a dry place at 15 - 30°C.

PHARMACOLOGY

ANIMALS

The anti-inflammatory effects of flurbiprofen have been demonstrated in several animal models. In the carrageenin-induced rat paw edema test the minimum effective dose was 0.11 mg/kg, with an ED_{50} of 4 mg/kg. At doses which inhibited edema, flurbiprofen caused a dose-dependent reduction in the numbers of leukocytes and prostaglandin concentration. In the preventive and established adjuvant arthritis rat tests the lowest effective dose was 0.17 mg/kg twice daily.

The analgesic activity dose-response curve in the mouse acetylcholine-writhing test was steep, with an ID_{50} (50% inhibition) at 0.3 mg/kg.

The antipyretic activity at doses of 0.12 - 1.0 mg/kg of flurbiprofen was demonstrated in the rat yeast-fever model. The body temperature of normal rats was not affected by flurbiprofen. Flurbiprofen, at a concentration of 8×10^{-6}M, caused a 50% inhibition of prostaglandin synthesis from arachidonic acid in a bovine seminal vesicle, microsomal prostaglandin synthetase preparation.
In the mouse liver glycogen deposition test, flurbiprofen had no glucocorticoid activity.

HUMANS

PHARMACOKINETICS

Following a single 100 mg oral dose of flurbiprofen tablets to healthy volunteers peak serum concentrations of 12.7 $\pm$ 2.8 mcg/mL are reached in 1.9 $\pm$ 0.7 hours. The apparent elimination half-life is 3.8 $\pm$ 0.4 hours. Multiple dose studies of 50 mg three times a day in volunteers results in no drug accumulation and steady state serum concentrations of 5 to 6 mcg/mL. Administration of a single 50mg dose of flurbiprofen to elderly men (age range 66 - 90 years) results in peak blood levels of 5 -6 mcg/mL, similar to those seen in young, healthy males.
Elderly females (74 - 94 years) have higher mean peak concentration of 8.7 $\pm$ 0.8 mcg/mL as compared to elderly and young males, however, this difference is not significant. These higher concentration levels are not related to a reduction in elimination of flurbiprofen since the half life of elimination is similar to that found in young, healthy male volunteers. The mean volume of distribution is lower in elderly females than in elderly or young males. The total amount of drug absorbed or the time to reach peak levels does not differ between age groups indicating that the rate of absorption is not altered with old age and thus the onset of action in geriatric patients is not delayed.

Flurbiprofen absorption is delayed up to 2 hours in some individuals when administered with food resulting in lower maximum plasma levels, but the total amount of drug absorbed is not affected by concomitant food intake.

In man, 20 - 25% of a dose of flurbiprofen is recovered from the urine as free and conjugated unchanged drug. Three major urinary metabolites have been identified with the most abundant being hydroxylation products, representing about 60 - 80% of the administered dose. At therapeutic blood levels, flurbiprofen is at least 99% bound to serum proteins. Excretion of Froben is completed 24 hours after the last dose.

FROBEN SR

Comparison of the AUC values for the sustained release capsules and conventional tablets show that the capsule has adequate bioavailability in most volunteers with no evidence of dose dumping or excessive accumulation of flurbiprofen. A steady state is reached within 2 to 3 days. The elimination half-life for flurbiprofen is 3 to 4 hours and is not significantly different following long term administration.

Pharmacokinetic parameters determined in elderly patients have been shown to be comparable with those seen in younger patients. Studies in which young and elderly patients received single daily doses of sustained release capsules resulted in a C_{max}, C_{max}^{ss}, AUC_{0-48} and AUC_{0-48}^{ss} of 7.53 mcg/ml, 10.33 mcg/ml, 134.0 mcg.h/ml and 192.7 mcg.h/ml, respectively in elderly patients compared to 8.56 mcg/ml, 10.78 mcg/ml, 138.5 mcg.h/ml and 195.5 mcg.h/ml, respectively in young patients.

The effect of food on Froben SR causes a delay in T_{max} (from 5.5 to 8.3 h), increases C_{max} significantly (to 10 ug/ml) and increases bioavailability. The AUC for the sustained release capsules increases to a figure close to that of conventional tablets (taken fasting).

TOXICOLOGY

Acute Toxicity

	LD_{50} (mg / kg)	
	Mouse	Rat
Oral	750	600
I.P.	200	---
I.V.	---	greater than 150

Signs of toxicity included CNS depression and delayed deaths from intestinal damage. Baboons tolerated doses up to 125 mg/kg with no adverse reactions. Beagle dogs had dose-

related GI reactions at does of 1 to 16 mg/kg.

Sub-acute Toxicity

Groups of 10 mice were administered flurbiprofen orally by intubation for 90 days at 1, 5 or 25 mg/kg. Hemoglobin was markedly reduced in males given 25 mg/kg daily and to a lesser, but significant, extent in those receiving 5 mg/kg. All females on the 25 mg/kg dose died of GI damage by the 8th week of administration. Two out of 10 males on the same dose died before the end of the study. There was no pathological evidence of GI damage in either males or females at the 1 and 5 mg/kg dose levels. Surviving male mice at the 25 mg/kg dose had liver and spleen hyperplasia and evidence of intestinal erosion.

Groups of 10 rats were given flurbiprofen by intubation at doses of 1, 5 or 25 mg/kg daily for 30 days. No pathological, blood chemistry or hematological changes were seen in the animals on the two lower doses.

At the 25 mg/kg dose both male and female rats showed a slight retardation of growth, enlarged spleen, and anemia.

Enlarged kidneys were seen in males only and thyroids in females only. Microscopic intestinal lesions were observed in some animals. During a three-week post-dosing recovery period, these abnormal reactions returned towards normal.

Oral doses of 0.25, 1 and 4 mg/kg of flurbiprofen were each administered to two cats for up to 30 days. GI hemorrhage and erosion occurred at all doses.

Groups of 2 Beagle dogs were given oral doses of 0.04, 0.2 or 1 mg/kg daily of flurbiprofen in two divided doses for 30 days. Animals on two lower doses had small gastric ulcers or erosions. Animals given l mg/kg had severe, bleeding gastric and duodenal ulcers, in some instance with perforations. They also demonstrated emesis, anorexia, weight loss, anemia, occult fecal blood and enlarged spleens.

Beagle dogs given flurbiprofen subcutaneously b.i.d. at a dose of 0.2 mg/kg daily for 30 days demonstrated more extensive G.I. damage than dogs receiving the same dose orally.

Two males and two female baboons each received oral flurbiprofen at daily doses of 1, 5 or 25 mg/kg for 30 days. Weight gain in the two low dose groups was less than for control

baboons and those receiving 25 mg/kg lost weight over the 4-week study period. Although all but one animal had hemoglobin levels in the normal range after dosing for 30 days, the reduction in mean values in animals receiving 5 and 25 mg/kg fell by 2 - 3 g%, compared to about 1 g% in control and animals given l mg/kg. Fecal occult blood was detected in 3 of 4 and 4 of 4 baboons ingesting 5 and 25 mg/kg flurbiprofen, respectively. Histopathological examination of various tissues did not show any abnormal findings which could be related to flurbiprofen.

Chronic Toxicity and Carcinogenicity

No significant effects on survival or general health of mice were noted in animals given oral doses of 2, 5 and 12 mg/kg of flurbiprofen for 80 weeks in their diet. Weight gain of the males on the high dosage were depressed. The incidence, time of onset and types of tumours observed were similar among treated and control groups and there was no evidence of carcinogenicity. Three groups of 12 newly-weaned rats were given 1, 5 or 25 mg/kg daily by intubation for 26 weeks. Compared to controls, small elevations in hemoglobin levels and reduced RBC counts and hematocrit were recorded. Females had elevated serum SGPT. Both males and females receiving the 25 mg/kg dose showed significant anemia by the fourth week of drug intake. All animals at this dose had histopathological evidence of GI pathology with severe intestinal ulceration. Rats on the 25 mg/kg dose had increased adrenal, heart, kidney, liver, lung and spleen weights. Renal papillary edema was seen in 8 of 12 females on the high dose, compared to 1 of 12 and 0 of 12 in the 5 and 1 mg/kg dose groups, respectively. Most animals on the high dose, and about half on the 5 mg/kg dose, had lymphoid hyperplasia with an inflammatory reaction. Moderate chronic inflammation of the liver was seen in the majority of animals receiving 25 mg/kg and in about half the animals ingesting 5 mg/kg.

In three groups of 6 baboons given 1, 5 or 25 mg/kg daily oral doses of flurbiprofen for six months in b.i.d. administration, no gross signs of toxicity were observed. One animal in each of the high and intermediate dose groups developed microcytic anemia. Occult fecal blood was found sporadically in most animals, with the frequency being greater in the high and intermediate dose animals than in low dose or control baboons. Acute gastric ulceration and erosions were found in all baboons given 5 and 25 mg/kg daily.

In a combined chronic toxicity and carcinogenicity study, rats were dosed orally with 2, 5 or 12 mg/kg daily for 2 years, except that the highest dose level was reduced to 5 mg/kg daily

from week 32 to 104. Mortality was higher in males (17.5%) and females (17.5%) in the high dose group during the first 32 weeks of flurbiprofen intake compared to control (0%), which persisted in the females even after the dose was reduced to 5 mg/kg/day.

Females receiving 5 mg/kg/day initially had an overall mortality of 73% over the 104 weeks, compared to 55% for control animals. Body weight gains in the high and middle dose groups were slightly depressed in males between week 6 and 60 and from week 60 onwards in the females. Both sexes in the 12 mg/kg dose group were anemic by week 27 and some females remained so until the end of the study. No blood biochemical changes of significance were noted, but kidney weights were elevated in females of all 3 groups and spleen weights increased in females in the 12 mg/kg group. Of 125 animals examined at the end of the study, extensive GI mucosal ulceration was seen in 3 females in the 12 mg/kg and one female in the 5 mg/kg/day dose groups. In decedents 26 of 34 females and 9 of 26 males in the 12 mg/kg dose group showed evidence of GI ulceration or necrosis of the ileal mucosa. Of the 16 decedent rats receiving 5 mg/kg/day, 5 females and 1 male exhibited intestinal lesions.

Various degrees of progressive glomerulonephrosis were seen in some animals from each group. A renal papillary lesion was reported in 1 rat in the low dose group and renal papillary necrosis was seen only in 1 rat in each of the low and middle dose groups and in 2 rats in the high dose group. No evidence of tumorigenicity was found at any dose level.

Reproductive Studies

Flurbiprofen given to Swiss mice orally at doses of 2, 5 or 12 mg/kg daily from day 3 to 18 of pregnancy had no teratogenic effects. The incidence of dead and resorbed progeny was 11.1% in the high dose group and 9.5% in control mice, thus there was no treatment related response. The proportion of litters containing fetuses with subcutaneous and visceral blood spots was greater in the treated groups than in the control group, although the relevance of this observation is not clear.

No teratogenic effect was seen in Wistar rats given daily oral doses of 2.25, 7.5, or 25 mg/kg from day 1 to day 20 of pregnancy. Some dams, at the high dose level died and others showed gastrointestinal ulceration, retardation of body weight gain and intrauterine hemorrhage. Litter sizes were normal but fetal weights were lower. No effects were seen

at the lower 2.25 and 7.5 mg/kg daily dose levels.

The effects of flurbiprofen on labour were investigated in rats given oral doses of 2.25, 7.5 or 25 mg/kg/day from day 1 of pregnancy until parturition. At all dose levels there was a prolongation of pregnancy by 1 - 3 days, an increase in uterine bleeding and deaths. There was an increase in stillbirths and a reduction in litter survival in all treatment groups.

In a second study rats were given oral flurbiprofen at doses of 0.2, 0.675 or 2.25 mg/kg/day from day 1 of pregnancy until delivery. An additional group of dams was given 2.25 mg/kg/day from day 1 to 16 of pregnancy. A dose of 0.2 mg/kg/day had no effect, but the results for the other dose levels were similar to those found in the first study. Rats given the 2.25 mg/kg daily from day 1 to 16 of pregnancy had pregnancies of normal length and their labours followed a normal course. Litters were similar in size and viability to those of control animals.

Gastric ulceration was observed in dams receiving 2.25 mg/kg daily or greater. No evidence of teratogenicity was seen in any dose group.

In a third study flurbiprofen was administered to female rats from day 16 of pregnancy to parturition at oral doses of 0.4, 1, 4, or 10 mg/kg daily. Animals in each dose group displayed a delay in the onset of labour, a prolongation of labour, an increase in stillbirths and gastric hemorrhage and ulceration in the dams. Flurbiprofen was not found to be teratogenic but it was embryotoxic. In a fertility study in Boots-Wistar rats male and female animals were given oral doses of 2.25 mg/kg daily for 65 and 16 days, respectively, before mating. No impairment in fertility in either sex was observed.

New Zealand white rabbits were administered oral doses of 0.675, 2.25, or 7.5 mg/kg daily from day 1 to 29 of pregnancy. On day 30 of pregnancy the rabbits were killed and their uterine contents examined. The implantation index, litter size and fetal mortality was the same in all surviving dose groups as for control rabbits. However, two dams receiving 7.5 mg/kg/day died from gastric ulceration and contained dead fetuses. There was no evidence of teratogenicity. All doses caused gastric ulcertain in the dams, which was most severe in the high dose group.

Administration of 0.2 mg/kg orally of flurbiprofen to Boots-Wistar rats daily throughout

pregnancy and lactation did not impair lactation or suckling as judged by survival and development of the young.

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