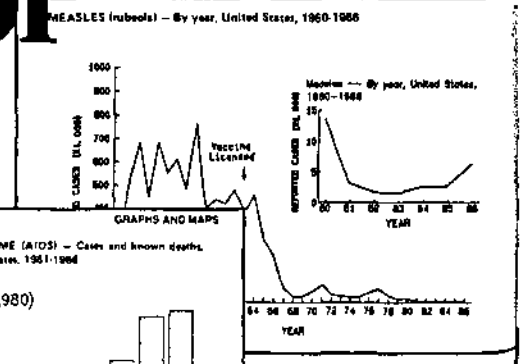
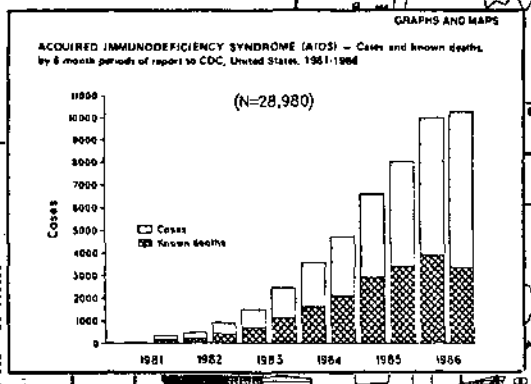
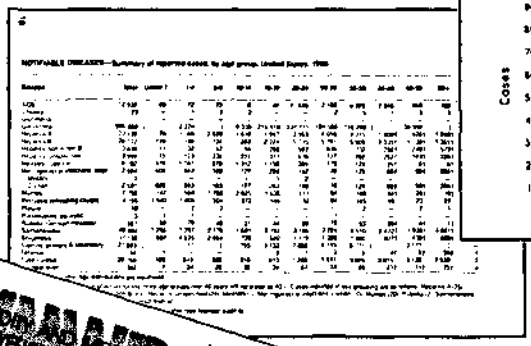
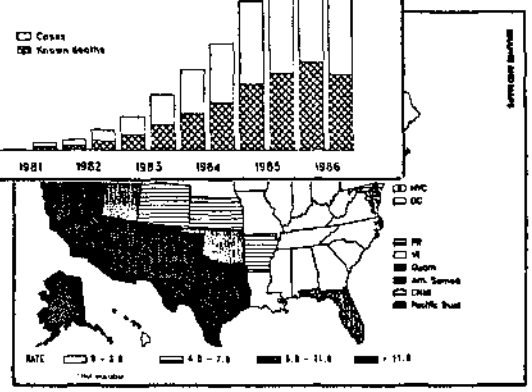
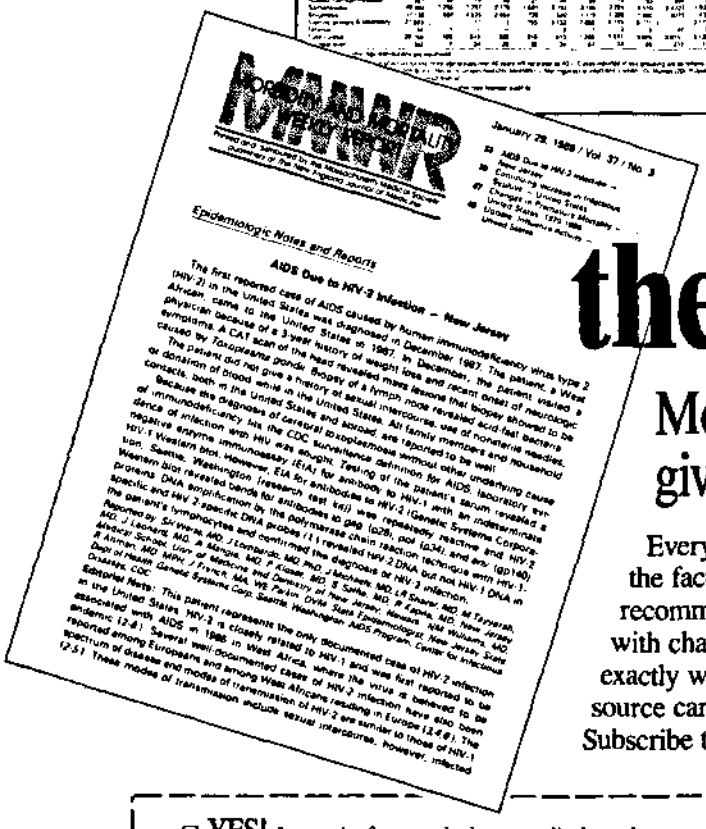
Your Best Lines of Defense Against Disease are the Facts











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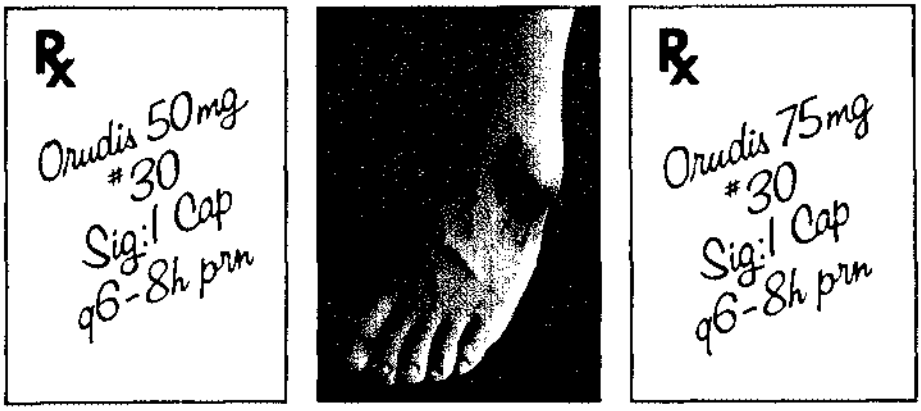

ORUDIS® STOPS THE PAIN THAT STOPS YOUR PATIENTS

(ketoprofen)

References: 1. Sunshine A, Olson NZ: Analgesic efficacy of ketoprofen in postpartum, general surgery, and chronic cancer pain. *J Clin Pharmacol* 1988;28(suppl):47-54. **2.** Stambaugh J, Drew J: A double-blind parallel evaluation of the efficacy and safety of a single dose of ketoprofen in cancer pain. *J Clin Pharmacol* 1988;28(suppl):34-39. **3.** Turek MD, Baird WM: Double-blind parallel comparison of ketoprofen [ORUDIS®], acetaminophen plus codeine, and placebo in postoperative pain. *J Clin Pharmacol* 1988;28(suppl):23-28. **4.** Cooper SA, Bernie R, Cohn P: Comparison of ketoprofen, ibuprofen, and placebo in a dental surgery pain model. *Adv Ther* 1988;5:43-53. [Additional material on file at Wyeth-Ayerst Laboratories.] **5.** Data on file, Wyeth-Ayerst Laboratories.

ORUDIS® (ketoprofen)

BRIEF SUMMARY OF PRESCRIBING INFORMATION:

Consult the package literature for full prescribing information.

CONTRAINDICATIONS: Hypersensitivity to ORUDIS. Do not give to patients in whom aspirin or other NSAIDs induce asthma, urticaria, or other allergic reactions, because severe, rarely fatal, anaphylactic reactions to ORUDIS were reported in such patients.

WARNINGS: RISK OF GI ULCERATION, BLEEDING, AND PERFORATION WITH NSAID THERAPY: Serious gastrointestinal toxicity (e.g., bleeding, ulceration, perforation) can occur at any time, with or without warning symptoms, during chronic NSAID therapy. Although minor upper-gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients on chronic NSAID therapy, even in the absence of previous GI-tract symptoms. In clinical trials symptomatic upper-GI ulcers, gross bleeding, or perforation appeared to occur in approximately 1% of patients treated 3 to 6 months, and in about 2-4% treated for one year. Physicians should inform patients of the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

To date, studies failed to identify any patient subset not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. The relative risk of various NSAIDs in causing such reactions is unknown. High NSAID doses probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

GENERAL PRECAUTIONS: ORUDIS and other NSAIDs cause nephritis in mice and rats with chronic administration. Cases of interstitial nephritis and nephrotic syndrome have been reported with ORUDIS since it has been marketed abroad. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have supportive role in maintenance of renal blood flow. In these patients use of an NSAID results in a dose dependent decrease in prostaglandin synthesis and, secondarily, in renal blood flow which may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, those on diuretics, and the elderly. Discontinuation of NSAID is typically followed by recovery to pretreatment state. Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics are altered by renal failure [see "Clinical Pharmacology" in package insert], patients with significantly impaired renal function should be closely monitored, and a reduction of dosage should be anticipated. As with other NSAIDs, borderline elevations of one or more liver-function tests may occur in up to 15%. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1%. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver test has occurred, should be evaluated for evidence of development of a more severe hepatic reaction while on ketoprofen. Serious hepatic reactions, including jaundice, have been reported from postmarketing experience with ketoprofen as with other NSAIDs. If steroid dosage is reduced or eliminated during therapy, it should be reduced slowly and patients observed closely for evidence of adverse effects, including adrenal insufficiency and exacerbation of arthritis. Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by NSAIDs, which may produce fluid retention or minor GI blood loss in some. Therefore, patients with initial hemoglobin values of 10 g/dL or less who are to receive long term therapy should have hemoglobin values determined frequently. Peripheral edema was observed in about 2%. Therefore, as with other and all NSAIDs, use ketoprofen with caution in patients with fluid retention, hypertension, or heart failure.

Information for Patients: Although rare, NSAID therapy may cause serious side effects, such as gastrointestinal bleeding, which may result in hospitalization or fatal outcomes. Physicians may wish to discuss with their patients the potential risks (see "Warnings," "Precautions," and "Adverse Reactions" sections) and likely benefits of NSAID treatment, particularly in those situations where acceptable alternative therapy is available.

Because aspirin causes increase in level of unbound ketoprofen, patients should not take aspirin while on ORUDIS [see "Drug Interactions"]. It is possible that minor adverse symptoms of GI intolerance may be prevented by giving ORUDIS with antacids, food, or milk. Antacids do not affect bioavailability but food and milk do affect rate but not extent of absorption [see "Clinical Pharmacology"]. Specific recommendations to patients about when to take ORUDIS in relation to food and/or what patients should do if they experience minor GI symptoms should be made.

Laboratory Tests: Because serious GI-tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up [see "Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy"].

Drug Interactions:

Diuretic. Patients on diuretics are at a greater risk of renal failure secondary to decreased renal blood flow caused by prostaglandin inhibition secondary to ORUDIS.

Warfarin. Because prostaglandins play an important role in hemostasis and ketoprofen affects platelet function as well, concurrent ORUDIS/warfarin therapy requires close monitoring.

Methotrexate: Increased toxicity due to displacement of protein-bound methotrexate is reported when NSAIDs are given with methotrexate.

Lithium. NSAIDs may increase steady-state plasma lithium levels; therefore, lithium levels should be monitored when ORUDIS is given with lithium.

Concurrent use of aspirin or probenecid with ketoprofen is not recommended.

Drug/Laboratory Test Interactions: Effect on Blood Coagulation: ORUDIS decreases platelet adhesion and aggregation and can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in mice did not indicate carcinogenic potential. A chronic oral toxicity study was performed in rats with no statistically significant increase in any tumor type; however, this study was unacceptable because of poor survival. ORUDIS did not show mutagenic potential in Ames Test. ORUDIS in male rats had no significant effect on reproductive performance or fertility. In female rats, decrease in number of implantation sites was noted.

Abnormal spermatogenesis or inhibition of spermatogenesis developed in rats and dogs at high doses, and a decrease in the weight of the testes occurred in dogs and baboons at high doses.

Teratogenic Effects: Pregnancy Category B: In teratology studies ORUDIS in mice and rats showed no teratogenic or embryotoxic effects. In separate studies in rabbits, maternally toxic doses were associated with embryotoxicity but not teratogenicity.

There are no adequate and well-controlled studies in pregnant women. Because animal teratology studies are not always predictive of human response, ORUDIS should be used in pregnancy only if potential benefit justifies risk.

Labor and Delivery: Effects of ORUDIS on labor and delivery in pregnant women are unknown. Studies in rats have shown ORUDIS to prolong pregnancy when given before onset of labor. Because of the known effects of prostaglandin-inhibiting drugs on fetal cardiovascular system (closure of ductus arteriosus), avoid use of ORUDIS in late pregnancy.

Nursing Mothers: Data on secretion in human milk after ingestion of ketoprofen do not exist. As with other drugs excreted in milk, ORUDIS is not recommended in nursing mothers.

Pediatric Use: ORUDIS (ketoprofen) is not recommended for children, because safety and effectiveness have not been studied in children.

ADVERSE REACTIONS: Incidence of common ADRs (>1%) was obtained from 835 ketoprofen-treated patients in double-blind trials lasting 4 to 54 weeks.

Minor GI side effects predominated, upper GI symptoms were more common than lower GI symptoms. Peptic ulcer or GI bleeding occurred in controlled clinical trials in <1% of 1,076 patients; however, in open label continuation studies in 1,292 patients rate was >2%. Incidence of peptic ulceration in patients on NSAIDs is dependent on many risk factors, including age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticoids, as well as dose and duration of treatment with NSAIDs (see "Warnings"). These were followed in frequency by CNS side effects, such as headache, dizziness, or drowsiness. The incidence of some ADRs appears to be dose-related (see "Dosage and Administration" in package insert).

Those rare adverse reactions (incidence <1%) were collected from foreign reports to manufacturers and regulatory agencies, publications, and U.S. clinical trials.

In double-blind trials, 733 ketoprofen-treated patients had fewer minor GI complaints, tinnitus and hearing impairment, fluid retention, and minor abnormalities in liver function tests than 228 aspirin-treated patients.

Incidence >1% (Probable Causal Relationship):

Digestive: Dyspepsia (11.5%), nausea*, abdominal pain*, diarrhea*, constipation*, flatulence*, anorexia, vomiting, stomatitis. *CNS*: Headache*, dizziness, CNS inhibition (i.e., pooled reports of somnolence, malaise, depression, etc.) or excitation (i.e., insomnia, nervousness, dreams, etc.).* *Special Senses*: Tinnitus, visual disturbance. *Skin and Appendages*: Rash. *Urogenital*: Impairment of renal function (edema, increased BUN)*, signs or symptoms of urinary-tract irritation.

*Side effects with incidence greater than 3%.

Incidence <1% (Probable Causal Relationship):

Digestive: Appetite increase, dry mouth, eructation, gastritis, rectal hemorrhage, melena, fecal occult blood, salivation, peptic ulcer, GI perforation, hematemesis, intestinal ulceration. *CNS*: Amnesia, confusion, impotence, migraine, paresthesia, vertigo. *Special Senses*: Conjunctivitis, conjunctivitis sicca, eye pain, hearing impairment, retinal hemorrhage and pigmentation change, taste perversion. *Skin and Appendages*: Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, bullous rash, exfoliative dermatitis, photosensitivity, skin discoloration, onycholysis. *Body as a Whole*: Chills, facial edema, infection, pain, allergic reaction, anaphylaxis. *Cardiovascular*: Hypertension, palpitation, tachycardia, congestive heart failure, peripheral vascular disease, vasodilation. *Hemic*: Hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia. *Metabolic and Nutritional*: Thirst, weight gain, weight loss, hepatic dysfunction, hyponatremia. *Musculoskeletal*: Myalgia. *Respiratory*: Dyspnea, hemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm, laryngeal edema. *Urogenital*: Menometrorrhagia, hematuria, renal failure, interstitial nephritis, nephrotic syndrome.

Incidence <1% (Causal Relationship Unknown):

(listed to serve as alerting information to physician) *Digestive*: Buccal necrosis, ulcerative colitis. *CNS*: Dysphoria, hallucination, libido disturbance, nightmares, personality disorder. *Body as a Whole*: Septicemia, shock. *Cardiovascular*: Arrhythmias, myocardial infarction. *Endocrine*: Diabetes mellitus (aggravated). *Metabolic and Nutritional*: Jaundice. *Urogenital*: Acute tubulopathy, gynecomastia.

OVERDOSAGE: Should a patient ingest a large number of capsules, empty stomach by gastric lavage or induction of vomiting and employ usual supportive measures. The drug is dialyzable, therefore, hemodialysis may be useful to remove circulating drug and assist in case of renal failure.

DOSAGE AND ADMINISTRATION: RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS. Starting dose 75 mg t.i.d. or 50 mg q.i.d. (range 150-300 mg daily).

MILD-TO-MODERATE PAIN AND DYSMENORRHEA. 25-50 mg q6-8h prn.

How supplied: 25, 50 and 75 mg capsules.

CI 3827-2 October 10, 1988

WYETH-AYERST LABORATORIES
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