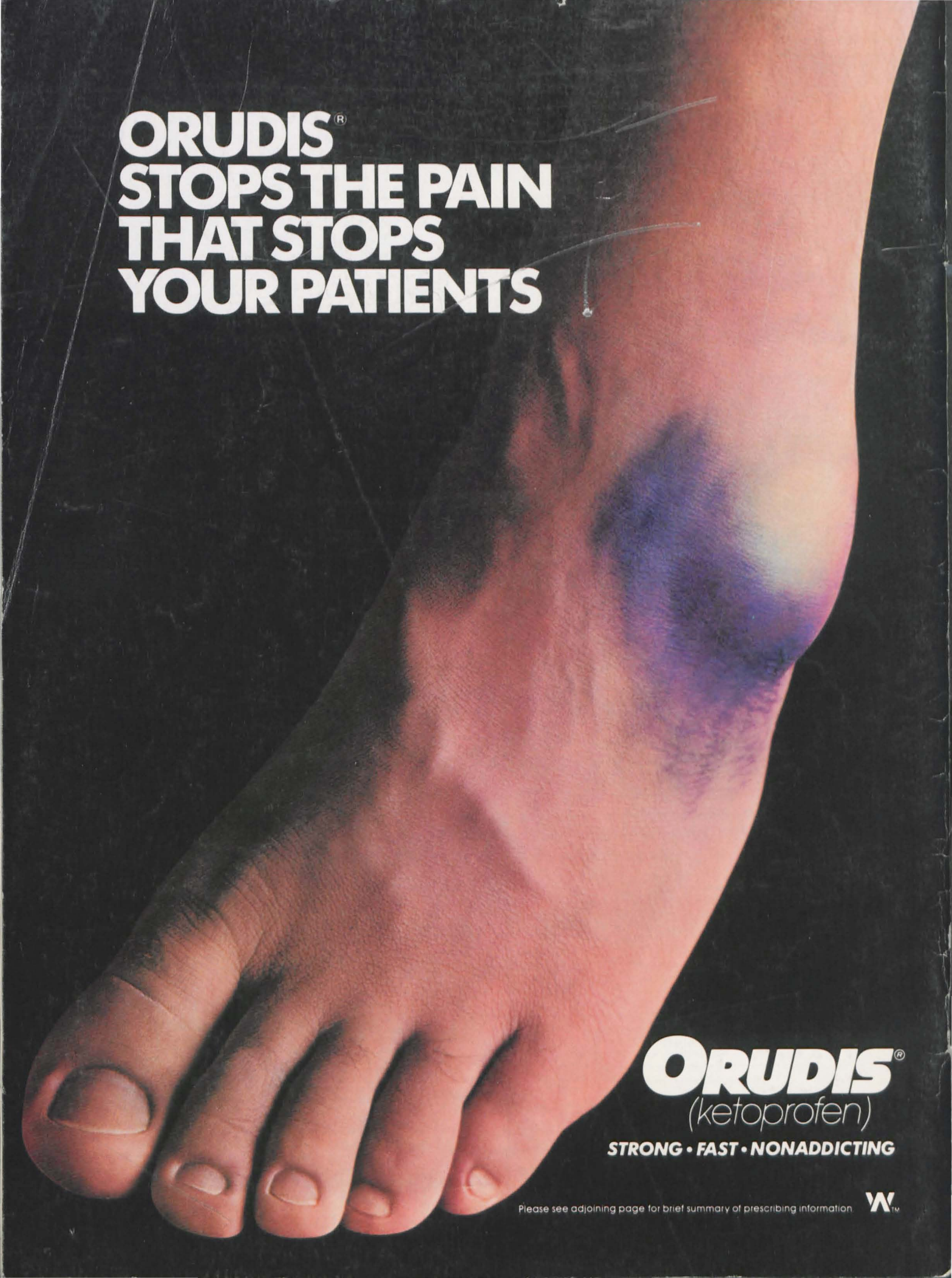
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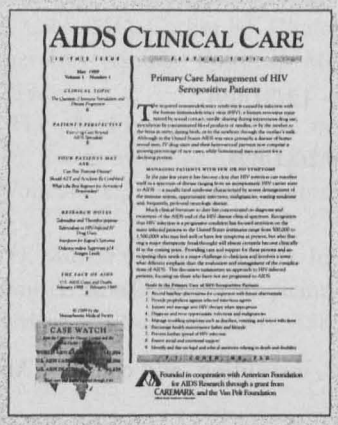
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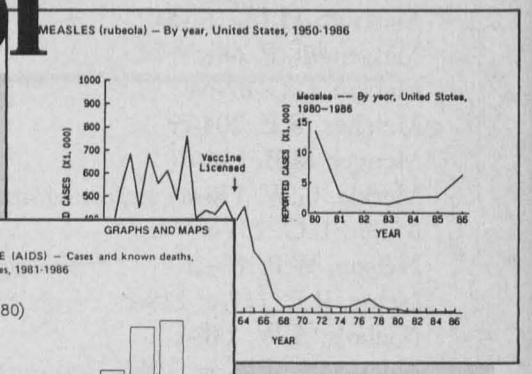

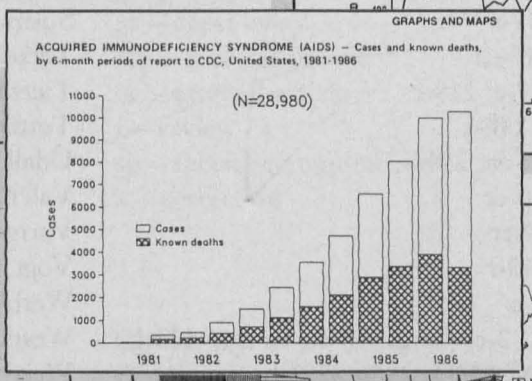

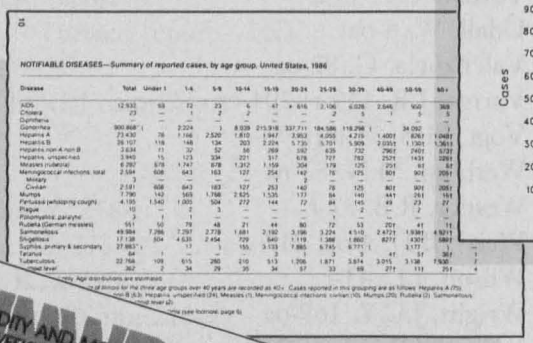

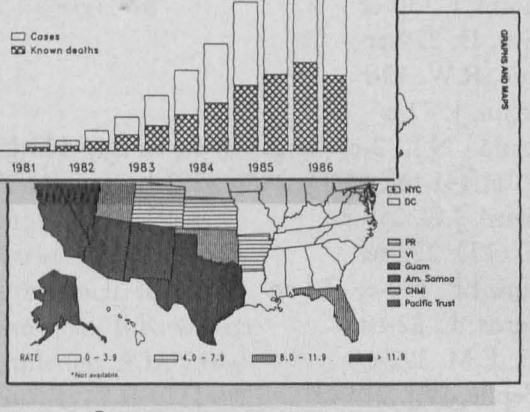

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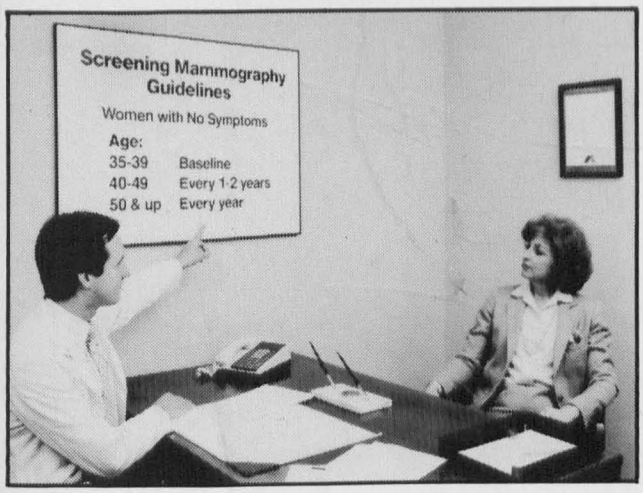

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ORUDIS® (ketoprofen)

BRIEF SUMMARY OF PRESCRIBING INFORMATION:

Consult the package literature for full prescribing information.

CONTRAINDICATIONS: Hypersensitivity to Orudis. Do not give if aspirin or other NSAIDs have induced asthma, urticaria, or other allergic reactions since fatal, anaphylactic reactions have been reported in such patients.

WARNINGS: RISK OF GI ULCERATION, BLEEDING, AND PERFORATION WITH NSAID THERAPY: Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur at any time, with or without warning symptoms during chronic therapy. Minor upper GI problems are common early in therapy but physicians should remain alert for ulceration and bleeding even without previous GI-tract symptoms. Occurrence of serious GI toxicity is about 1% after 3-6 months of therapy, 2-4% after a year. Patients should be informed of signs and symptoms of serious GI toxicity and what to do if it occurs. Studies have failed to identify a patient subset not at risk. Prior history of serious GI events and other risk factors of peptic ulcer disease (e.g., alcoholism, smoking, etc.) are the only factors associated with increased risk. Elderly and debilitated patients tolerate ulceration or bleeding less well and have more fatal GI events. High doses probably carry a greater risk. Consider benefit versus risk (of GI toxicity) in prescribing higher recommended doses.

PRECAUTIONS: Chronic administration of NSAIDs causes nephritis in mice and rats. Interstitial nephritis and nephrotic syndrome have been reported with Orudis since it has been marketed abroad. A second form of renal toxicity is seen in patients having reduced renal blood flow or blood volume, where prostaglandins support the maintenance of renal blood flow. In these patients NSAIDs cause a dose-dependent decrease in prostaglandin synthesis and renal blood flow which may precipitate overt renal failure. Patients with impaired renal or hepatic function, heart failure, those on diuretics, or the elderly are at greatest risk. Discontinuation of NSAIDs typically leads to recovery. Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics altered by renal failure, patients with impaired renal function should be closely monitored to identify a needed dosage reduction. Borderline elevations of liver-function tests may occur in up to 15% and may progress, remain unchanged, or disappear with continued therapy. Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated further as serious hepatic reactions, including jaundice, have been reported. SGPT (ALT) is the most sensitive indicator of liver dysfunction. To reduce or eliminate steroid dosage during therapy, go slowly and look closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of arthritis. Anemia is common in rheumatoid arthritis and sometimes aggravated by NSAIDs. Patients with initial hemoglobin of 10 g/dL or less should have hemoglobin values determined frequently during chronic therapy. Peripheral edema was seen in about 2% of Orudis patients, so use caution in patients with fluid retention, hypertension, or heart failure.

Information for Patients: Physicians should discuss potential risks (See Warnings, Precautions, Adverse Reactions) and likely benefits with patients especially when other drugs offer an acceptable alternative for less serious conditions. Advise patients what to do if they experience major or minor GI symptoms. Minor GI symptoms are sometimes prevented by giving Orudis with food, milk, or antacids. (Note that antacids do not affect bioavailability; food and milk affect rate but not extent of absorption.) Advise patients not to take aspirin while on Orudis.

Drug Interactions:

Diuretic: Patients on diuretics are at greater risk of renal failure secondary to decreased renal blood flow due to prostaglandin inhibition (See Precautions).

Warfarin: Because prostaglandins are important in hemostasis and ketoprofen also affects platelet function, concurrent Orudis/warfarin therapy requires close monitoring.

Methotrexate: Co-administration of methotrexate and NSAIDs has caused methotrexate toxicity due to displacement of protein-bound methotrexate.

Lithium: Increased steady-state plasma lithium levels. Lithium levels should be monitored when given with Orudis.

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 about 3 to 4 minutes. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic or mutagenic potential. No impairment of reproduction or fertility seen in male rats. Female rats had decreased number of implantation sites. Rats and dogs had inhibition of, or abnormal, spermatogenesis at high doses, and dog and baboon testes decreased in weight.

Teratogenic Effects: Pregnancy Category B: No effects seen in mice. Maternally toxic doses in rabbits produced embryotoxicity but not teratogenicity.

Use not recommended in pregnancy.

Labor and Delivery, Nursing Mothers, Pediatric Use: Use is not recommended.

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

Minor GI side effects predominated; more upper GI symptoms noted than lower GI. In controlled clinical trials peptic ulcer or GI bleeding noted in <1% of 1,076 patients; open-label studies in 1,292 patients had rate >2%. Peptic ulceration incidence in patients on NSAIDs depends on many risk factors, e.g., age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticoids, plus dose and duration of treatment with NSAIDs. Next in frequency were CNS side effects such as headache, dizziness, or drowsiness. Incidence of some ADRs appears dose-related (See Dosage and Administration in package insert).

In double-blind trials, 233 patients on Orudis had fewer minor GI complaints, tinnitus and hearing impairment, fluid retention, and minor liver function test abnormalities 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 as information to alert physicians) *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: Reports are rare. Symptoms usually mild or absent. Vomiting and drowsiness have occurred. With large doses, empty stomach by gastric lavage or induced vomiting and use required support therapy. Orudis® is dialyzable; thus, hemodialysis may remove circulating drug or assist in 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. **Keep tightly closed. Dispense in tight container.**

CI 3827-2 October 10, 1988

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