Information for Authors

These guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." (The complete document is available in the June 12, 1982, issue of the *British Medical Journal* and the June 1982 issue of the *Annals of Internal Medicine.)*

Manuscripts

Manuscripts containing original material are accepted for consideration with the understanding that neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted for publication elsewhere before appearing in the *Journal*. This restriction does not apply to abstracts or press reports published in connection with scientific meetings. Copies of any possibly duplicative manuscripts should be submitted to the Editor along with the manuscript that is to be considered by the *Journal*. The *Journal* strongly discourages the submission of more than one article dealing with related aspects of the same study. In almost all cases, a single study is best reported in a single paper.

Submit an original and one copy of the complete manuscript, including text pages, legends, tables, references, and glossy prints of figures. Only typed copy, on standard-sized typewriter paper and double-spaced throughout, with margins of at least 2.5 cm, is acceptable. Address all submissions to the Editor, *The Journal of the American Board of Family Practice*, 2228 Young Drive, Lexington, KY 40505. A covering letter should identify the person (with the address and telephone number) responsible for negotiations concerning the manuscript; the letter should make it clear that the final manuscript has been seen and approved by all authors.

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The *Journal* will print measurements in Système International (SI) and conventional units (this practice applies only to clinical investigation and review articles). Authors may use either as their principal system; however, they must also provide the alternative numbers and units in parentheses.

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With the manuscript, provide a page giving the title of the paper; a running head of fewer than 40 letter spaces; the name(s) of the author(s), including the first name(s) and academic degree(s); the name of the department and institution in which the work was done; and the name and address of the author to whom reprint requests should be addressed. Any grant support that requires acknowledgment should be mentioned on this page.

Abstracts

Use another page to provide an abstract of not more than 175 words. This abstract should be factual, not descriptive, and should present the reason for the study, the main findings (give specific data if possible), and the principal conclusions.

Key Words

The *Journal* has a policy of requiring authors to submit two to four key words with their manuscripts, to be used for purposes of classification by subject.

References

References must be typed in double spacing and numbered consecutively as they are cited. References first cited in tables or figure legends must be numbered so that they will be in sequence with references cited in the text. The style of references is that of the *Index Medicus*. List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al." Sample references are as follows:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide. N Engl J Med 1979; 301:1382-5.
2. Beam AG. Wilson's disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basis of inherited disease. New York: McGraw-Hill, 1972:1033-50.
3. Pellegrin FA, Ramcharan S, Fisch IR, Phillips NR. The noncontraceptive effects of oral contraceptive drugs: the Kaiser-Permanente Study. In: Ramcharan S, ed. The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives. Vol. 1. Bethesda, Md.: National Institutes of Health, 1974:1-19. (DHEW publication no. (NIH)74-562).

Numbered references to personal communications, unpublished data, and manuscripts either "in preparation" or "submitted for publication" are unacceptable (see "Permissions"). If essential, such material may be incorporated in the appropriate place in the text.

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Type tables in double spacing on separate sheets, and provide a legend for each. Excessive tabular data are discouraged. If an article is accepted, the *Journal* will arrange to deposit extensive tables of important data with the National Auxiliary Publications Service (NAPS); we will pay for the deposit and add an appropriate footnote to the text. This service makes microfiche or photocopies of tables available at moderate charges to those who request them.

Illustrations

Figures should be professionally designed. Glossy, black-and-white photographs are requested. Symbols, lettering, and numbering should be clear, and these elements should be large enough to remain legible after the figure has been reduced to fit the width of a single column.

The back of each figure should include the sequence number, the name of the author, and the proper orientation (e.g., "top"). Do not mount the figure on cardboard. Photomicrographs should be cropped to a width of 8 cm, and electron photomicrographs should have internal scale markers.

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permission to use the figure. Permission forms are available from the Editor.

Legends for illustrations should be typewritten (double-spaced) on a separate sheet, and should not appear on the illustrations.

Color illustrations are used from time to time. Send both transparencies and prints for this purpose.

Abbreviations

Except for units of measurement, abbreviations are discouraged. Consult the *Council of Biology Editors Style Manual* (Fifth edition. Bethesda, Md.: Council of Biology Editors, 1983) for lists of standard abbreviations. The first time an abbreviation appears it should be preceded by the words for which it stands.

Drug Names

Generic names should, in general, be used. If an author so desires, brand names may be inserted in parentheses.

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Review and Action

Manuscripts are examined by the editorial staff and are usually sent to outside reviewers. Authors will remain anonymous to outside reviewers and vice-versa. External statistical review will be accomplished where appropriate.

Conversion Factors to Système International Units for Selected Laboratory Components.

System*	Component	"Old" Unit	Conversion	"New" Unit
S	acetoacetate	mg/dL	97.95	μmol/L
B, S	acetone	mg/dL	172.2	μmol/L
S	albumin	g/dL	10	g/L
P	ammonia (NH_3)	μg/dL	0.5872	μmol/L
S	amylase	U/L units/dL	0.01667	μkat/L
S	bilirubin	mg/dL	17.1	μmol/L
S	calcium	mg/dL	0.2495	mmol/L
B, P, S	carbon dioxide content (bicarbonate + CO_2)	mEq/L	1.00	mmol/L
S	chloride	mEq/L	1.00	mmol/L
P	cholesterol	mg/dL	0.02586	mmol/L
S	creatine	mg/dL	76.25	μmol/L
S	creatinine	mg/dL	88.40	μmol/L
S, U	creatinine clearance	mL/min	0.01667	mL/s
P	digoxin	ng/mL	1.281	nmol/L
B	erythrocyte count (RBC)	$10^6/mm^3$	1	$10^{12}/L$
P	ethanol	mg/dL	0.2171	mmol/L
P	fibrinogen	mg/dL	0.01	g/L
P	glucose	mg/dL	0.05551	mmol/L
B	hematocrit	%	0.01	0.00
B	hemoglobin			
	massc.	g/dL	10	g/L
	substc. Hb (Fe)	g/dL	0.6206	g/L
S	immunoglobins			
	IgG	mg/dL	0.01	g/L
	IgA	mg/dL	0.01	g/L
	IgM	mg/dL	0.01	g/L
	IgD	mg/dL	10	mg/L
	IgE	IU/mL	2.4	μg/L
P, S	insulin	μg/mL	172.2	pmol/L
S	iron	μg/dL	0.1791	μmol/L
B	leukocyte count (WBC)	mm^{-3}	0.001	$10^9/L$
	numfr. (differential)	%	0.01	1
S	lipase	U/L	0.01667	μkat/L
P	lipids, total	mg/dL	0.01	g/L
P	lipoproteins	mg/dL	0.02586	mmol/L
S	magnesium	mg/dL	0.4114	mmol/L

*P represents plasma; B, blood; S, serum; U, urine.

Abbreviations used: massc., mass concentration; numfr, number fraction; substc., substance concentration; substfr., substance fraction (mole fraction).

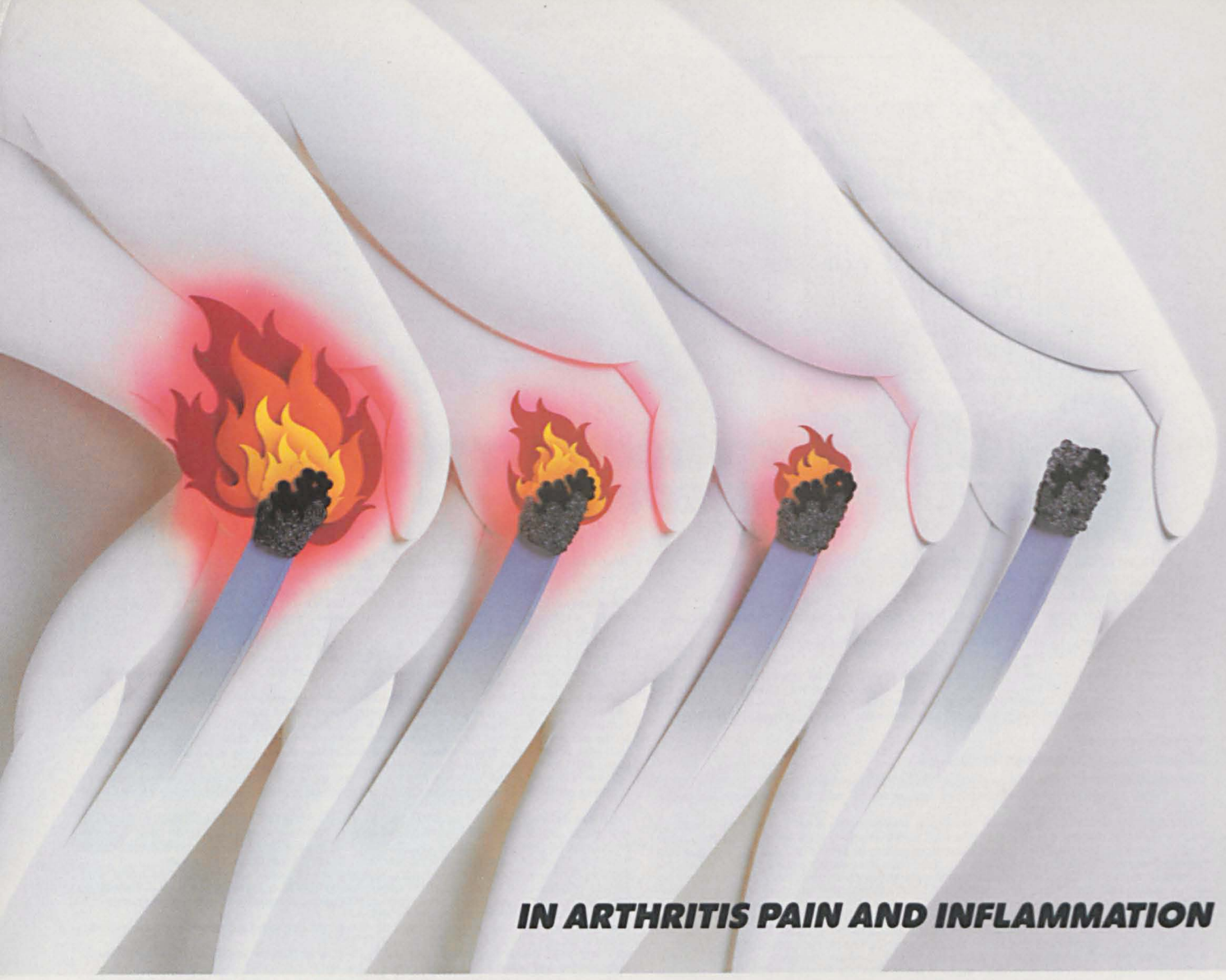
(Continued on next page)

Conversion Factors to Système International Units for Selected Laboratory Components (continued from previous page).

System*	Component	"Old" Unit	Conversion	"New" Unit
B	mean corpuscular hemoglobin (MCH)			
	massc.	pg	1	pg
	substc. Hb (Fe)	pg	0.06206	fmol
B	mean corpuscular hemoglobin concentration (MCHC)			
	massc.	g/dL	10	g/L
	substc. Hb (Fe)	g/dL	0.6206	mmol/L
B	mean corpuscular volume (MCV) Erc volume	um^3	1	fL
U	osmolality	mOsm/kg	1.00	mmol/kg
B	oxyhemoglobin, substfr. "oxygen saturation"	%	0.01	mol/mol (= 1)
S	phosphate (as phosphorus)	mg/dL	0.3229	mmol/L
S	potassium	mEq/L	1.00	mmol/L
S	protein, total	g/dL	10	g/L
S	sodium	mEq/L	1.00	mmol/L
U	steroids			
	17-hydroxycorticosteroids (as cortisol)	mg/24 h	2.759	μmol/d
	ketosteroid fractions			
	androsterone	mg/24 h	3.443	μmol/d
	dehydroepiandrosterone	mg/24 h	3.467	μmol/d
	etiocholanolone	mg/24 h	3.443	μmol/d
B	thrombocytes (platelets)	$10^3/mm^3$	1	$10^9/L$
S	thyroid tests			
	thyroid stimulating hormone	μU/mL	1.00	mU/L
	thyroxine (T4)	μg/dL	12.87	nmol/L
	thyroxine binding globulin (TBG)	μg/dL	12.87	nmol/L
	thyroxine, free	ng/dL	12.87	pmol/L
S	urea nitrogen	mg/dL	0.3570	mmol/L urea
S	uric acid	mg/dL	59.5	mmol/L
S	vitamin B_{12}	pg/mL	0.7378	pmol/L

*P represents plasma; B, blood; S, serum; U, urine.

Abbreviations used: massc., mass concentration; numfr, number fraction; substc., substance concentration; substfr., substance fraction (mole fraction).



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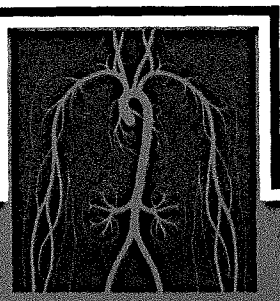

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Recommended as a first-line therapy

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Calan® SR

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The only calcium antagonist indicated for hypertension

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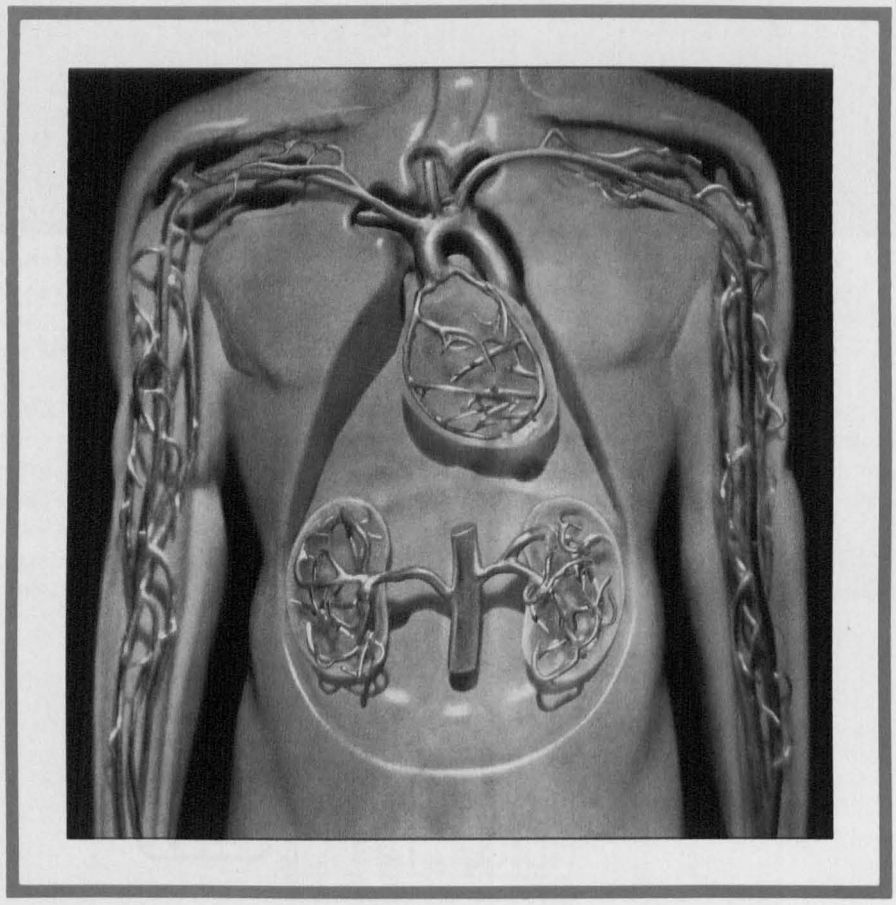

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- Over one-half million patients nationwide take Calan SR; approximately 80% of all office-based cardiologists and primary care physicians nationwide have prescribed Calan SR

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FIRST-LINE THERAPY THAT MEETS EXPANDED ANTIHYPERTENSIVE GOALS

The only once-a-day calcium antagonist*

- Convenient one-caplet, once-a-day dosing regimen.* Start with one 240-mg caplet in the morning *with food* (which promotes slow and smooth absorption). Starting dosages of 120 mg/day, ½ caplet, may be suitable for the elderly or for those of small stature.

Contraindications: severe left ventricular dysfunction, hypotension or cardiogenic shock, sick sinus syndrome, second- or third-degree AV block, atrial flutter or atrial fibrillation and an accessory bypass tract, known hypersensitivity to verapamil HCl.

*Some patients may require *b.i.d.* dosing.

CALAN® SR (verapamil HCl) SUSTAINED-RELEASE CAPLETS 240 mg

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

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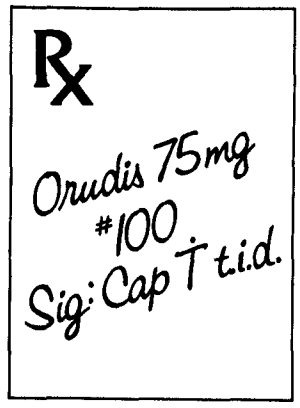

ORUDIS® (ketoprofen)

SEE HOW FAST YOUR PATIENTS IMPROVE

As with most NSAIDs, the primary excretion route of ORUDIS is the kidney, and patients with impaired renal function may need dosage adjustments. See General Precautions in the Package Insert.

*Naprosyn® (naproxen), Feldene® (piroxicam), and Motrin® (ibuprofen) are registered trademarks of Syntex Laboratories, Pfizer Laboratories, and The Upjohn Company, respectively.

†Peptic ulcer or GI bleeding occurred in controlled clinical trials in less than 1% of patients; however, in open label continuation studies, the rate was greater than 2%.

References: 1. Caldwell JR, Germain BF, Lourie SH, et al: Ketoprofen versus indomethacin in patients with rheumatoid arthritis: A multicenter double-blind comparative study. *J Rheumatol*, in press. **2.** Data on file, Wyeth-Ayerst Laboratories. **3.** Manufacturers' Prescribing Information. **4.** Cooper SA, Berrie R, Cohn P: Comparison of ketoprofen, ibuprofen, and placebo in a dental surgery pain model. *Advances in Therapy* 1988;5:43-53.

ORUDIS® (ketoprofen)

BRIEF SUMMARY OF 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: As with other steroidal and nonsteroidal antiinflammatory drugs, peptic ulcerations and GI bleeding have been reported with ORUDIS. Unlike most adverse reactions, which are usually manifest in first month if they occur, new peptic ulcers keep appearing in patients on ORUDIS at a rate >2% per year (see "Adverse Reactions"). In patients with GI bleeding or active peptic ulcer, institute appropriate anti-ulcer regimen and weigh benefits of ORUDIS vs possible hazards and closely monitor patient's progress. When given to patients with a history of GI disease, give under careful supervision and only after consulting "Adverse Reactions" section.

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 to avoid accumulation of ketoprofen and/or its metabolites. 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: 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 (see "Drug Interactions") 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.

Drug Interactions: These were studied with ORUDIS doses of 200 mg/day (50 mg q.i.d.). The possibility of increased interaction should be kept in mind when ORUDIS doses greater than 50 mg as a single dose or 200 mg/day are used concomitantly with highly bound drugs.

1. *Antacids:* Concomitant magnesium hydroxide and aluminum hydroxide do not interfere with rate or extent of ketoprofen absorption.

2. *Aspirin:* ORUDIS use does not alter aspirin absorption; however, in a study of 12 normal subjects, concurrent administration of aspirin decreased ketoprofen protein-binding and increased ketoprofen plasma clearance from 0.07 L/kg/hr without aspirin to 0.11 L/kg/hr with aspirin. Clinical significance of these changes has not been adequately studied. Therefore, concurrent use of aspirin and ketoprofen is not recommended.

3. *Diuretic:* Hydrochlorothiazide, given concomitantly with ORUDIS, produces reduction in urinary potassium and chloride excretion compared to HCTZ alone. Patients on diuretics are at greater risk of renal failure secondary to decrease in renal blood flow caused by prostaglandin inhibition (see "General Precautions").

4. *Digoxin:* In a study in 12 patients with CHF where ORUDIS and digoxin were given concomitantly, ORUDIS did not alter digoxin serum levels.

5. *Warfarin:* In a short-term controlled study in 14 normal volunteers, ORUDIS did not significantly interfere with the effect of warfarin on prothrombin time. Bleeding from a number of sites may be a complication of warfarin and GI bleeding a complication of ORUDIS. Because prostaglandins play important role in hemostasis and ketoprofen has an effect on platelet function as well (see "Blood Coagulation"), concurrent therapy with ORUDIS and warfarin requires close monitoring.

6. *Probenecid:* Increases both free and bound ketoprofen through reducing plasma clearance of ketoprofen as well as decreasing protein-binding. Combination of ORUDIS and probenecid is not recommended.

7. *Methotrexate:* Avoid coadministration of ORUDIS and methotrexate because increased toxicity due to displacement of protein-bound methotrexate is reported when NSAIDs are given with methotrexate.

8. *Lithium:* NSAIDs have been reported to increase steady-state plasma lithium levels. Plasma lithium levels should be monitored when ORUDIS is given with lithium.

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 (up to 32 mg/kg/day) did not indicate carcinogenic potential (maximum recommended human therapeutic dose for a 50 kg man is 6 mg/kg/day). A chronic oral toxicity study was performed in rats (up to 12.5 mg/kg/day) 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 (up to 9 mg/kg/day) had no significant effect on reproductive performance or fertility. In female rats given 6 or 9 mg/kg/day, 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 at doses up to 12 mg/kg/day and rats at doses up to 9 mg/kg/day, approximate equivalent of 1.5 times the maximum recommended therapeutic dose in (a 50 kg) man, 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 at 6 mg/kg (approximately equal to maximum recommended human dose) 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: In rats, ORUDIS at 9 mg/kg (approximately 1.5 times maximum human dose) did not affect perinatal development. In lactating dogs, milk concentration of ORUDIS was found to be 4 to 5% of plasma drug level. 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 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, 233 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: Reports are rare. Of 20 subjects reported in Great Britain (5 children, 14 adolescents or young adults, and 1 man 80-years-old), only 4 had mild symptoms (vomiting in 3, drowsiness in 1 child). Highest reported dose was 5,000 mg in the elderly man who displayed no symptoms.

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. **Keep tightly closed. Dispense in tight container.**

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

WYETH-AYERST LABORATORIES
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