Disalcid B.I.D.

(salsalate) 750 mg

A Radical Improvement Over Aspirin.

BRIEF SUMMARY

CONTRAINDICATIONS. DISALCID is contraindicated in patients hypersensitive to salsalate

WARNINGS. Reye Syndrome may develop in individuals who have chicken pox, influenza, or flu symptoms. Some studies suggest a possible association between the development of Reye Syndrome and the use of medicines containing salicylate or aspirin. DISALCID contains a salicylate and therefore is not recommended for use in patients with chicken pox, influenza, or flu symptoms.

chicken pox, influenza, or flu symptoms.

PRECAUTIONS. General Precautions. Patients on long-term treatment with DISALCID should be warned not to take other salicylates so as to avoid potentially toxic concentrations. Great care should be exercised when DISALCID is prescribed in the presence of chronic renal insufficiency. Protein binding of salicylic acid can be influenced by nutritional status, competitive binding of other drugs, and fluctuations in serum proteins caused by disease (rheumatoid arthritis, etc.). Laboratory

Tests. Plasma salicylic acid concentrations should be periodically monitored during long-term treatment with DISALCID to aid maintenance of therapeutically effective levels: 10 to 30 mg/100 ml. Toxic manifestations are not usually seen until plasma concentrations exceed 30 mg/100 ml (see OVERDOSAGE). Urinary pH should also be regularly monitored sudden acidification, as from pH 6.5 to 5.5, can double the plasma level, resulting in toxicity. Drug Interactions. Salicylates antagonize the uricosuric action of drugs used to treat gout. Aspirin and other salicylate drugs will be additive to DISALCID and may increase plasma concentrations of salicylic acid to toxic levels. Drugs and foods that raise urine pH will increase renal clearance and urinary excretion of salicylic acid, thus tions of salicylic acid to toxic levels. Drugs and foods that raise urine pH will increase renal clearance and urinary excretion of salicylic acid, thus lowering plasma levels; acidifying drugs or foods will decrease urinary excretion and increase plasma levels. Salicylates may competitively displace anticoaquiant drugs from plasma protein binding sites and thereby predispose to systemic bleeding. Salicylates may enhance the hypoglycemic effect of oral antidiabetic drugs of the sulfonylurea class. Salicylate competes with a number of drugs for protein binding sites, notably penicillin, thiopental, thyroxine, triiodothyronine, phenytoin, sulinpyrazone, naproxen, warfarin, methotrexate, and possibly corticosterioids. Drug Laboratory Test Interactions. Salicylate competes with thyroid hormone for binding to plasma proteins, which may be reflected in a depressed plasma T, value in some patients; thyroid function and basal metabolism are unaffected. Carcinogenesis. No long-term animal studies have been performed with DISALCID to evaluate its carcinogenic potential; however, several such studies using aspirin and other basal metabolism are unaffected. Carcinogenesis. No long-term animal studies have been performed with DISALCID to evaluate its carcinogenic potential; however, several such studies using aspirin and other salicylates have failed to demonstrate any association of these agents with cancerous cell changes. Use in Pregnancy, Pregnancy Category C: Salsalate and salicylic acid have been shown to be teratogenic and embryocidal in rats when given in doses 4 to 5 times the usual human dose. These effects were not observed at doses twice as great as the usual human dose. There are no adequate and well-controlled studies in pregnant women. DISALCID should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Labor and Delivery. There exist no adequate and well-controlled studies in pregnant women. Although adverse effects on mother or infant have not been reported with DISALCID use during labor, caution is advised when anti-inflammatory dosage is involved. However, other salicylates have been associated with prolonged gestation and labor, maternal and neonatal bleeding sequelae, potentiation of narcotic and barbiturate effects (respiratory or cardiac arrest in the mother), delivery problems and stilibrith. Nursing Mothers. It is not known whether salisalate per se is excreted in human milk; salicylic acid, the primary metabolite of DISALCID has been shown to appear in human milk in concentrations approximating the maternal blood level. Thus, the infant of a mother on DISALCID therapy might ingest in mother's milk 30 to 80% as much salicylate per kg body weight as the mother is taking. Accordingly, caution should be exercised when DISALCID is administered to a nursing woman. Pediatric Use. Satety and effectiveness in children have not been established.

ADVERSE REACTIONS. Auditory system. Tinnitus and temporary hearing loss can occur. Tinnitus probably represents blood salicylic acid levels reaching or exceeding the upper limit of the therapeutic range. It is therefore a helpful guide to dose titration. Temporary hearing loss disappears gradually upon discontinuation of the drug. Gastrointestinal system. Nausea, dyspepsia and heartburn occur occasionally.

DRUG ABUSE AND DEPENDENCE. Drug abuse and dependence have not been reported with DISALCID.

OVERDOSAGE. No deaths after overdosage have been reported for DISALCID. Death has followed ingestion of 10 to 30 g of other salicylates in adults, but much larger amounts have been ingested without fatal

The oral LD50 for DISALCID in rats is approximately 2000 mg/kg (sixty times the recommended maximum single dose for adults)

Symptoms. The usual symptoms of salicylism — tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting and diarrhea — will occur. More severe intoxication will lead to disruption of electrolyte balance and blood pH, and hyperthermia and dehydration.

Treatment. Further absorption of DISALCID from the G.I. tract should be prevented by emesis (syrup of ipecac) and, if necessary, by gastric lavage.

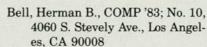
Fluid and electrolyte imbalance should be corrected by the administration of appropriate I.V. therapy. Adequate renal function should be maintained. Hemodialysis or peritoneal dialysis may be required in extreme

REFERENCES: 1. Fassett WE: Gastrointestinal intolerance to anti-inflammatory drugs: Is salsalate an exception? Pract Gastroenterol 1984;8:35-40. 2. April PA, Curran NJ, Ekholm BP, et al: Multicenter comparative study of salsalate vs aspirin in rheumatoid arthritis, abstracted. Arthritis Rheum 1987;30(4):S93.

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In hypertension...





Each tablet contains:

TENORMIN* (atenoloi) 50 mg or 100 mg and chlorthalidone 25 mg

Added control and convenience... without added side effects in a majority of patients... regardless of age, race, sex, and prior therapy.

TENORETIC is not indicated for the initial therapy of hypertension. See adjacent page for brief summary of prescribing information.

Added control and convenience ...without added side effects in a majority of patients...regardless of age, race, sex, and prior therapy.1

ONE TABLET A DAY enoretic

TENORMIN® (atenolol) 50 mg or 100 mg and chlorthalidone 25 mg

Please consult complete product information before prescribing. A summary follows:

TENORETIC (atenolol and chlorthalidone) is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a beta₁-selective (cardioselective) hydrophilic blocking agent (atenolol, TENORMIN*) and a monosulfonamyl diuretic (chlorthalidone).

Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch

INDICATIONS AND USAGE: TENORETIC is indicated for the treatment of hypertension. This fixeddose combination drug is not indicated for initial therapy of hypertension. If the fixed-dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS: TENORETIC is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure (see WARNINGS), anuria, hypersensitivity to this product or to sulfonamide-derived drugs.

hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics. TENORETIC should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients receiving TENORETIC should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. It cardiac failure continues despite adequate digitalization and diuretic therapy. TENORETIC therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys, TENORETIC should be used to talk the with impaired renal function.

kidneys, TENORETIC should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident.

TENORETIC should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. TENORETIC should be used with caution in these

patients.

Ischemic Heart Disease: Although not yet reported with atenolol following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of an agent and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORETIC is planned, the patient should be activated to limit physical activity to a minimum.

TENORETIC should be reinstated if withdrawal symptoms occur.

TRONDRETIC should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁-selectivity, however, TENORETIC may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta₂-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs, it may be decided to withdraw TENORETIC before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents because of the risk of further depression of the myocardium.

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE). Manifestations of excessive vagal tone (eg, prolound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Metabolic and Endocrine Effects: TENORETIC may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged, latent diabete patients when the processing and the processing that the diabete patients was beingressed, and excessing that the diabete decreased, and excessed, or unchanged, latent diabete patients may be increased, decreased, or unchanged, latent Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN

Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent

insulin requirements in diabetic patients may be increased, decreased, or unchanged, latent diabetes mellitus may be become manifest during chlorthalidone administration. Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected developing thyrotoxicosis and from whom TENORETIC therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, TENORETIC should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide

PRECAUTIONS, General—Electrolyte and Fluid Balance Status: Periodic determination of serum

electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance; ie, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or toods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponaltremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponaltremia is life-threatening. In actual salt relations, appropriate represented is the therapy of choice.

rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Drug Interactions: TENORETIC may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with TENORETIC plus a catecholamine depletor (eg., reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with TENORETIC.

Should it be decided to discontinue therapy in patients receiving TENORETIC and clonidine concurrently, the TENORETIC should be discontinued several days before the gradual withdrawal of deciding.

Condine.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient

posisympamectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study with atenoici, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents.

Atenoici was negative in the mouse dominant tethal test, the Chinese hamster in vivo cytogenetic

test and the Salmonella typhimurium back mutation test (Ames test), with or without metabolic

activation.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Use in Pregnancy: Pregnancy Category C. TENORETIC (atenolol and chlorthalidone) was studied for teratogenic potential in the rat and rabbit. Doses of 10, 100 and 300 mg/kg/day were administered orally to pregnant rats, with no teratologic effects observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 10, 100 or 200 mg/kg/day. No teratologic changes were noted; embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose). In a second rabbit study, dosages were 5, 10 and 25 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 25 mg/kg/day (approximately) 12.5 times the maximum recommended human dose) or greater. TENORETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atenoloj—Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions

only if the potential benefit justifies the potential risk to the fetus.

<u>Atenolo</u>—Atenolo has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in abbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Chlorthalidone—Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving TENORETIC.

Pediatric Use: Safety and effectiveness in children have not been established.

TENORETIC.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TENORETIC is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for TENORETIC are essentially the same as those seen with the individual components.

Atenolol: The frequency estimates that follow derive from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebotreated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and place to similar causal relationship to atenolol is uncertain.

atenoiol and placebo is similar, causal relationship to atenoiol is uncertain.

The data present these estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

side effects) and then from both US and foreign studies (volunteered and elicited side effects): US STUDIES (% ATENDIOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), latigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.5%), depression (0.6%-0.5%), draeming (0%-0%), opperation (0.6%-0.5%), drowsiness (0.6%-0.5%), draming (0%-0.0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: hardwardia (3%-0%), opid extremities (12%-5%), postural hypotension

TOTALS US AND FOREIGN STÜDIES:
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), litedness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal; anorexia, gastric irritation, Chiormandone: Cardiovascular: ortnostatic hypotension, Castrointestinal; anorexia, gastric irritation, vomiting, cramping, constippation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; CNS: vertigo, paresthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia: Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no new or upospected advance effects.

unexpected adverse effects. In addition, a variety of adverse effects not observed in clinical trials with atenolo lbut reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of atenolo. Nervous System: reversible mental depression progressing to catatonia; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics; Cardiovascular: intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal; mesenteric arterial thrombosis, ischemic collists; Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura, Allergic: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Miscellaneous: reversible alopecia, Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TENORETIC or TENORMIN (atenolol).

Clinical Laboratory Past Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TENORETIC. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uncacid and decreases in serum potassium.

most common changes were increases in uric acid and decreases in serum potassium.

DOSAGE AND ADMINISTRATION: Initial dose should be one TENORETIC 50 tablet once a day. If optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet

optimal response is not achieved, the dosage should be increased to one I ENOHE. It C 100 tablet once a day. Package insert should be consulted for dosage adjustments in cases of severe impairment of renal function.

HOW SUPPLIED: TENORETIC 50 Tablets (atenolol 50 mg and chlorthalidone 25 mg). NDC 0310-0115 (white, round, biconvex, uncoated tablets with ICI on one side and 115 on the other side, bisected) are supplied in bottles of 100 tablets.

TENORETIC 100 Tablets (atenolol 100 mg and chlorthalidone 25 mg). NDC 0310-0117 (white, round, biconvex, uncoated tablets with ICI on one side and 117 on the other side) are supplied in bottles of 100 tablets.

Protect from heat, light, and moisture. Dispense in well-closed, light-resistant container.

A/12/86

Reference: 1. TENORETIC Evaluation Program, an open 28-day study of 26,892 hypertensive patients conducted by more than 7,000 physicians (data on file, ICI Pharma, Wilmington, Delaware): physicians were requested to enter those patients needing more control than provided by

