18-647

Summary Basis of Approval

NDA 18-647

Applicant:
E. R. Squibb and Sons, Inc.
New Brunswick, New Jersey

Drug Generic Name:
Nadolol-Bendroflumethiazide

Drug Trade Name:
Corzide

I. Indications for Use:

Corzide is indicated in the management of hypertension.

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

II. Dosage form, route of administration and recommended dosage:

Tablets contain the following ingredients:

Nadolol 40 mg, Bendroflumethiazide 5 mg.
or
Nadolol 80 mg, Bendroflumethiazide 5 mg.

Dosage Recommendation:

DOSAGE MUST BE INDIVIDUALIZED.
CORZIDE MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.

Bendroflumethiazide is usually given at a dose of 5 mg daily. The usual initial dose of nadolol is 40 mg once daily whether used alone or in combination with a diuretic.

The initial dose of Corzide (Nadolol-Bendroflumethiazide Tablets) may therefore be the 40/5 mg tablet once daily. When the antihypertensive response is not satisfactory, the dose may be increased by administering the 80/5 mg tablet once daily.

When necessary, another antihypertensive agent may be added gradually, beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Dosage Adjustment in Renal Failure - Absorbed nadolol is excreted principally by the kidneys and, although nonrenal elimination does occur, dosage adjustments are necessary in patients with renal impairment. The following dose intervals are recommended.

Creatinine Clearance (ml/min/1.73 m^2)	Dosage Interval (hours)
50	24
31-50	24-36
10-30	24-48
10	40-50

III. Manufacturing and Controls:

A. Manufacturing and Controls

The manufacturing and controls are adequately described and sufficient to characterize the product and assure its identity, strength, quality and purity.

B. Stability

Data submitted for the new drug substances and the finished tablets is adequate to support the proposed 2 year expiration date for this product.

C. Methods Validation

The analytical assay methods have been independently validated by an FDA Laboratory and have been found to be satisfactory for control and regulatory purposes.

D. Labeling

The immediate container labels for the 40/5 and 80/5 mg tablets are in compliance with requirements for proprietary name, non-proprietary name, potency statement, control number, prescription caution, expiration date and applicant's name and address.

E. Establishment Inspection

Facilities for both the manufacturers of the raw materials and finished tablets have been inspected and found to be in conformance with GMPs.

F. Environmental Impact Analysis Report

A statement is included that the operating procedures for the designated manufacturers of both the raw material and finished tablets are in compliance with all applicable requirements for the control of environmental emissions.

IV. Pharmacology:

A. Pharmacodynamics:

Pharmacodynamic interaction studies were not conducted nor were there new data on the single ingredients developed. The pharmacology of the two components of Corzide® (the beta — adrenoceptor blocker nadolol and the diuretic bendroflumethiazide) is known from their respective NDAs.

B. Toxicology:

Acute Oral Interaction Study in Mice

Charles River CD-1 outbred albino male mice (weighing 19.5-22.5 g) were given graded oral doses of nadolol in combination with a fixed oral dose of bendroflumethiazide. Both compounds were administered as 20% suspensions in 0.15% agar. Doses of nadolol ranged from 1300 to 7000 mg/kg and the fixed dose of bendroflumethiazide was 2000 mg/kg. The compounds were also given alone. There were 15 mice/group and the observation period lasted 8 days.

The oral LD_{50} of nadolol in combination with bendroflumethiazide was similar to the LD_{50} of nadolol alone (both approximately 4000 mg/kg). There was thus no evidence of potentiation of acute toxicity. Mice given nadolol alone or in combination had ataxia and convulsions in 5 minutes to 2 hours after dosing with the incidences proportional to dose. All deaths occurred within 24 hours, at which time survivors appeared normal. Mice given bendroflumethiazide alone showed no overt toxic signs.

Six Month Oral Administration Study in Dogs

Nadolol or bendroflumethiazide or both were administered, in gelatin capsules, to groups of 3 male and 3 female (14-41 month old) Beagle dogs once daily, 7 days a week, for 6 months as follows:

Group 1	160 mg nadolol/kg + 20 mg bendroflumethiazide/kg
Group 2	40 mg nadolol/kg + 5 mg bendroflumethiazide/kg
Group 3	160 mg nadolol/kg + 00 mg bendroflumethiazide/kg
Group 4	00 mg nadolol/kg + 20 mg bendroflumethiazide/kg
*Group 5	00 mg nadolol/kg + 00 mg bendroflumethiazide/kg

*empty capsules

Criteria for evaluation included survival, body weight changes, food and water consumption, excreta, physical condition, behavior, ECG, ophthalmoscopy and results of clinical lab tests (hematology, serum chemistry, urinalysis) and of gross and histopathologic examination of tissues (including organ weight determinations).

One high dose combination female was found dead on day 147 of study, about 1.5 hours after dosing. This animal had shown a moderately decreased serum K in week 13. Death was not attributed to treatment. Both combinations were associated with slight increases in serum GOT during the 5th week (only) and slight increases in serum LDH after 3 and 6 months of dosing. Determination of LDH isoenzymes at the end of the dosing period revealed that the elevation in serum LDH was due to increases in LDH_4 and LDH_5, suggesting a possible effect on liver or skeletal muscle, but gross and histopathologic examinations did not reveal any changes attributable to administration of either drug. All nadolol treated groups showed slight to moderate decreases in heart rate and in systolic and mean arterial pressure. The high dose combination group showed slight decreases in serum glucose. The group receiving bendroflumethiazide alone showed a slight decrease in serum potassium concentration throughout the study; changes in serum K were not seen in groups that also received nadolol. At necropsy mean adrenal gland weights of males given the high dose of bendroflumethiazide with or without nadolol were slightly higher than those of controls.

Six Month Oral Administration Study in Rats

Nadolol or bendroflumethiazide or both (freshly prepared solutions or suspensions in 0.05% Tween 20) were administered by gavage to groups of 10 male and 10 female (three week old) CR-CD rats, once daily, 7 days a week, for six months as follows:

Group 1	1000 mg nadolol/kg	+	125 mg bendroflumethiazide/kg
Group 2	160 mg nadolol/kg	+	20 mg bendroflumethiazide/kg
Group 3	1000 mg nadolol/kg	+	00 mg bendroflumethiazide/kg
Group 4	00 mg nadolol/kg	+	125 mg bendroflumethiazide/kg
*Group 5	00 mg nadolol/kg	+	00 mg bendroflumethiazide/kg

*12.5 ml of 0.05% Tween 20/kg daily

Criteria for evaluation included survival, body weight changes, excreta, physical condition, behavior, ophthalmoscopy and results of clinical lab tests (hematology, serum chemistry, urinalysis) and of gross and microscopic evaluation of tissues (including organ weight determinations).

There were 5 deaths, none of which were attributed to the administration of drug, but rather to dosing accidents or infection. One-thousand mg nadolol/kg, alone or in combination, was associated with excessive salivation after dosing, brownish colored urine (males) after the 15th week,

moderate decrease in weight gain (males), slight increases in serum glucose, and increased water consumption, urine output and urinary Na excretion. At necropsy, dose related incidences of distention of cecum were observed in nadolol treated groups. Nadolol, by itself, was associated with slight increases in serum K and serum Mg (latter in females only).

Bendroflumethiazide, alone or in combination with nadolol, was associated with very slight increases in serum urea nitrogen, a slight decrease in serum K, moderate decreases in serum Mg and increased adrenal gland weight (latter in males only). Female rats in all treated groups showed slight increases in serum Ca and in urinary potassium excretion.

Teratology Study in Rats

Freshly prepared solutions or suspensions of nadolol or bendroflumethiazide or both were given by gavage to four groups of 24 mated female CR-CD rats (about 10 weeks of age) days 7 through 16 of gestation. Once daily administrations were at the following dose levels:

Group 1	1000 mg nadolol/kg	+	125 mg bendroflumethiazide/kg
Group 2	150 mg nadolol/kg	+	20 mg bendroflumethiazide/kg
Group 3	1000 mg nadolol/kg	+	00 mg bendroflumethiazide/kg
Group 4	000 mg nadolol/kg	+	125 mg bendroflumethiazide/kg

A control group received a volume of vehicle equivalent to that given to the high dosage group (12.5 ml/kg).

Observations for survival, appearance and behavior were made daily. On day 21 the dams were killed and the fetuses taken by cesarian section. A detailed examination was made of the uteri and other organs of these dams. The following determinations were made: numbers of live, dead and resorbed fetuses, their location in the uterine horns and individual fetal and placental weights. In addition, the crown-rump length and trans-umbilical distance (of viable pups) were measured. Each pup was examined externally for malformations. Half of the pups were eviscerated, processed and subsequently subjected to detailed skeletal examination. The remainder were processed for examination under the stereomicroscope for soft tissue anomalies.

Under the conditions of this study, neither nadolol or bendroflumethiazide, nor the combination had adverse effects upon the dam at any of the dose levels tested. There was a significant reduction in mean fetal size and placental weight with the high dosage combination and a slight reduction in mean placental weight with the low dosage combination. No other evidence of embryotoxicity, fetotoxicity or teratogenicity was found.

V. Medical:

A. Introduction

Results from earlier clinical trials, conducted by the sponsor while developing nadolol, showed that when nadolol was added to hydrochlorothiazide an additional fall in blood pressure occurred. There is a reasonably large general experience involving the use of beta blockers and thiazide type diuretics. Nadolol and bendroflumethiazide were used in combination in an open study involving 2,302 patients. Both Nadolol and bendroflumethiazide are approved drugs and are marketed worldwide. No particular safety issues exist.

The combination product is supported by data from 2 bioavailability/pharmacokinetic studies and 2 adequate and well controlled clinical trials. Published accounts of other studies also support the combination.

B. Clinical Pharmacology

New clinical pharmacology studies were confined to studies of pharmacokinetics/bioavailability. Two 3-way crossover studies, each involving 24 normal healthy male volunteers compared the bioavailability of the 2 tablets that are to be marketed with their components. The comparisons are shown in the following table.

Protocol 17,789-2	Protocol 17,789-3
a) Corzide (2 tablets, each containing 40 mg nadolol and 5 mg bendroflumethiazide).	a) Corzide (1 tablet, containing 80 mg nadolol and 5 mg bendroflumethiazide).
b)Nadolol (2 tablets, each containing 40 mg).	b) Nadolol (1 tablet containing 80 mg).
c) Bendroflumethiazide (2 tablets, each containing 5 mg).	c) Bendroflumethiazide (1 tablet containing 5 mg).

Based on plasma level areas under the curve, nadolol in the combination tablet and in the marketed single entity tablet are equally bioavailable. Bendroflumethiazide in the combination tablet is approximately 30% more bioavailable than that in the marketed single entity tablet.

C. Well Controlled Clinical Trials

1. Protocol 11,976-20

Fourteen investigators studied 200 patients in a multicenter, double blind randomized, parallel design, trial, (protocol 11,976-20), which compared the effects of nadolol and bendroflumethiazide administered together with each of the drugs alone. Analysis of antihypertensive effects was based on the results of treatment in 195 patients of whom 66 were randomly assigned to the combination, 72 to the thiazide, and 59 to nadolol alone. Active, double-blind treatment lasted 8 weeks. At the end of the 8 week period, an open-label, dose reduction was allowed.

All patients had a primary diagnosis of essential hypertension and supine diastolic blood pressures between 100 and 120 mmHg after 4 weeks of placebo washout. Patients on a sodium restricted diet were allowed to continue on that diet throughout the study. Patients with any condition that contraindicated the use of a beta-blocker such as heart failure or asthma or heart block were excluded from the study.

Table 1 lists the fourteen investigators who carried out the study and the number of patients each studied. Most investigators studied only a few patients, with the maximum being 31 patients.

The specific formulations used in the study were a 5 mg bendroflumethiazide plus 80 mg nadolol tablet, a 5 mg bendroflumethiazide and placebo tablet, and an 80 mg nadolol plus placebo tablet.

Thirteen patients were excluded from evaluation of efficacy in this study: 4/70 of the patients assigned to the combination, 3/73 of those assigned to the thiazide and 6/65 of those assigned to nadolol alone. Table 2 indicates the reasons for exclusion of each patient. The comparison of the response to the three treatments is thus based on the results in 66 patients on the combination, 70 on bendroflumethiazide alone, and 59 patients on nadolol alone. A patient was included in the analysis only if he had received the assigned regimen for at least 4 weeks.

The last blood pressure reading recorded during the lead-in period at the time of randomization was used as a baseline. A table of the distribution of patients in the three treatment groups according to their baseline supine blood pressures is shown in Table 3; the groups were comparable. Tables 4a and 4b show that the groups were comparable with respect to sex, age, weight, and race. Table 5 shows the mean blood pressures at entry and at the end of the placebo lead-in period.

All 66 patients who received the combination for at least four weeks completed the full eight weeks of active therapy. Of the 70 patients who received thiazide alone and the 59 patients who received nadolol, alone 3 and 4 patients respectively completed at least four weeks but did not complete the study.

Patients whose blood pressure did not apparently respond to treatment had their doses increased in a double blinded fashion by the investigator. Approximately half of the patients treated with 5 mg of bendroflumethiazide alone had an inadequate blood pressure response which required an increase in dosage. Only 36% of those who received nadolol and 18% of those who received a combination required an increased dosage. These results were shown in Table 6.

Tables 7 and 7a show the statistical results for diastolic and systolic blood pressure at weeks 4, 6, and 8 of therapy in the supine and standing position and the adjusted change in blood pressure (adjusted for investigators and for differences in pre-treatment levels as a percent) for all the patients in the study. The combination had a greater effect on blood pressure than either of its ingredients from weeks 4 to 8. This is particularly evident in standing geometric mean blood pressure. It should be noted that the increased dosage after 4 weeks had no effect in the nadolol or combination groups and little effect, if any, in the thiazide group, suggesting that in this population titration beyond 80 mg nadolol or 5 mg bendroflumethiazide is usually not helpful.

All patients were categorized on the basis of supine diastolic blood pressure as either A) normalized, that is, supine diastolic blood pressure (SDBP) of 90 mm Hg or less, B) as a responder, not normalized, but at least a 10% decrease in SDBP from baseline, C) nonresponder, not normalized and less than 10% decrease in SDBP from baseline. During week 4 (Table 8a) approximately 67% of the patients could be placed in the normalized group who were on the combination drugs, whereas only 39% and 36% of patients could be considered normalized who were on the bendroflumethiazide or nadolol alone, respectively. Also important was the fact that 54% and 48% of patients on thiazide or nadolol alone, respectively, were considered nonresponders at the end of week 4 whereas only 24% were nonresponders on the combination therapy. These results were more dramatic at week 8 (Table 8b) when only 8% of the patients on the combination were considered nonresponders; 82% had their blood pressures normalized by the combination therapy. It should be noted that the advantage of the combination persisted even though there was more up titration of the thiazide-only and nadolol-only groups.

At the conclusion of the 8 weeks of active therapy patients were permitted to enter a long term study of combination therapy at the discretion of the investigator. Patients who received nadolol or bendroflumethiazide during the short term portion of this study were to be switched to the combination for the long term study in an unblinded fashion. Of the 203 patients who entered the active phase of treatment 107 continued on long term therapy. Of these 107 patients only 2 continued on nadolol alone and 3 on bendroflumethiazide alone. Each investigator adjusted the dose of nadolol and bendroflumethiazide according to the individual patient's need. The range of doses employed during the long term therapy is shown in Table 9.

Blood pressure of each patient, recorded at one month intervals, was compared with blood pressure at the end of the short term therapy and at the end of placebo lead-in. The summarized results are shown in Table 10. For patients receiving the combination tablet during short term (end S-T) and during the long term extension (mean BP end month), blood pressure were indistinguishable. For those patients receiving single entity, short term therapy (those on nadolol alone or bendroflumethiazide alone were pooled for this analysis), switching to the combination tablet improved blood pressure control.

The data shown in Table 11 indicate that patients either on nadolol or the combination (that is patients taking a beta-blocking agent), had a decreased heart rate. As expected the patients on the combination had less of a fall in heart rate than on nadolol alone, presumably because the diuretic and/or direct vasodilating effects of the thiazide tends to cause tachycardia. The patients on thiazide alone, as also expected, had a slight increase in heart rate.

All 203 randomly assigned patients were included in the evaluation of clinical safety. The safety analysis was divided into two sections: Adverse Reactions and Clinical Laboratory Findings.

Drug Related Adverse Reactions, Short Term Therapeutic Discontinuances: Thirty-nine patients observed drug related adverse reactions: 15 on the combination, 12 on the thiazide and 12 on nadolol alone. During the short term portion of the study, therapy was discontinued in seven patients, 3 of whom were on thiazide alone and 4 on nadolol alone. The adverse reactions noted are shown in Table 10. Lethargy seemed to be somewhat more common in the combination group.

Discontinuance on Single Entity Therapy: Of the three patients who were discontinued while receiving bendroflumethiazide, one experienced severe dizziness, nausea and vomiting, another also experienced episodes of nausea and vomiting, and the third experienced weakness and dizziness on standing with a standing blood pressure of 91/77 mmHg.

Of the four patients who were discontinued while receiving nadolol alone, one experienced shortness of breath due to asthma, another had moderate to severe diarrhea, another experienced orthostatic hypotension, and the fourth complained of dry mouth, dyspnea, and chest pain.

Long Term Discontinuance of Patients: Only one patient taking the combination therapy, a 55 year old black male who experienced mild orthostatic dizziness after the first week of therapy while receiving 5 mg of thiazide a day, was discontinued from therapy. He was entered into the combination phase of therapy, nevertheless, with no further adverse effects. During the second month of combination therapy, however, while receiving 5 mg of thiazide and 80 mg of nadolol the patient developed severe hyperglycemia which the investigator felt was "secondary to nadolol." Supine blood pressure had fallen to 130/88 mmHg. No followup data is available and the patient had no history of diabetes.

2. VA Cooperative Study

The Veterans Administration cooperative studies program, conducted one study, Edward D. Freis, M.D., Senior Medical Investigator. The study was sponsored by E. R. Squibb and Sons.

This was a double-blind, randomized trial involving 365 men with mild to moderate hypertension. The trial studied the blood pressure effects of nadolol plus placebo (doses of 80 to 240 mg, once a day, orally) in 81 patients, bendroflumethiazide plus placebo (doses of 5 to 10 mg once a day, orally) in 132 patients or nadolol plus bendroflumethiazide in 152 patients. Of the 365 randomized patients 308 completed the nadolol plus bendroflumethiazide part of the study.

The study started with a 2 to 8 week washout, followed by a 2 to 4 week placebo, baseline period. During this 2 to 12 week prerandomization period 115 patients were dropped from the study because the blood pressure was too low or too high, or patients were noncompliant to medication or clinic visits (480 patients entered the trial). Randomization required untreated sitting diastolic pressure between 95 and 114 mmHg on 2 successive visits, 80 to 110% of prescribed number of tablets were taken (established by pill count) and there was an absence of major cardiovascular complications or other serious systemic disease.

Active medication (nadolol, bendroflumethiazide, or a combination of the two) was continued for 12 weeks. At the end of the 12 week active medication period, patients whose blood pressure was not controlled (i.e., diastolic blood pressure less than 90 mmHg) received hydralazine in doses ranging from 25 to 100 mg twice daily). The unequal randomization was purposeful in order to have more patients receiving nadolol available to also receive hydralazine. The hydralazine results are not important to this approval and are not recounted here, although addition of hydralazine resulted in an additional blood pressure fall.

In the group receiving nadolol alone had 49% of the patients reach the goal of less than 90 mmHg diastolic blood pressure. For bendroflumethiazide 46% reached goal blood pressure and for the combination 85% reached goal blood pressure. Actual mean changes from baseline are shown in Table 4b. As can be seen whites fared better with nadolol alone and blacks fared better with bendroflumethiazide alone. In the whole population and in blacks, the combination was significantly superior to the components. In whites, in this study, the combination was superior to both components for systolic pressure but was not distinguishable from nadolol in its effect on diastolic pressure.

Overall Evaluation and Conclusions:

Approval of the fixed dose combination product containing nadalol and bendroflumethiazide rests upon the following:

a. Results of one multicenter clinical trial involving 195 evaluable patients with hypertension showed the specific combination of nadolol plus bendroflumethiazide to be more effective than either nadolol or bendroflumethiazide alone. The results from each center were consistent with the pooled results although no single center was able to stand on its own.

b. Results of a second multicenter (VA Cooperative Trial) involving 308 evaluable patients with hypertension also showed the specific combination of nadolol plus bendroflumethiazide to be more effective than either nadolol or bendroflumethiazide alone.

c. Results of 2 bioavailability studies, conducted in normal volunteers, showed that nadalol in currently marketed single entity tablets and nadolol in the combination were equally bioavailable. The studies also showed that bendroflumethiazide in the combination is about 30% more bioavailable than that of the currently marketed single entity. The increased bioavailability, and failure of patients in the non-VA multicenter study to have 5 mg of bendroflumethiazide or more than 80 mg nadolol provides a good reason to limit the dose of the combination to a single 5 mg thiazide 80 mg nadolol dose.

d. Animal data with respect to the specific combination of nadalol and bendroflumethiazide raise no specific issues with respect to the specific combination.

e. The components of the new combination have not been specifically titrated to see what dose of each would be optimal, but the doses used are well within the range recommended for the single ingredients.

D. Advisory Committee Actions

There was no advisory committee consultation.

E. Post-Marketing Studies

The lack of good dose-response information for the components will be corrected in post-marketing studies agreed to by the sponsor.

F. Labeling

Approved labeling is attached.

TABLE 1
INVESTIGATORS

INVESTIGATOR (Number, Name and Address)	NUMBER OF PATIENTS							
	REJECTED IN LEAD-IN	INCLUDED			EXCLUDED			TOTAL
		NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	
0508 Roy A. Wiggins, M.D. 105 Collier Road, N.W. Atlanta, GA 30309	0	5	6	5	2	0	2	20
1837 Theodore S. Herman, M.D. Veterans Administration Hospital 3495 Bailey Avenue Buffalo, NY 14215	1	3	3	4	0	0	0	11
2287 Ronald R. Baratta, M.D. 672 North Wellwood Avenue Lindenhurst, NY 11757	1	8	9	9	0	0	0	27
3085 Arthur A. Sasahara, M.D. Veterans Administration Hospital 1400 Veterans of Foreign Wars Pkwy. West Roxbury, MA 02132	2	6	8	7	0	0	1	24

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		NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	
4239 Louis S. Ferris, M.D. 30 Central Park South New York, NY 10019	8	0	0	0	0	0	0	8
5215 Mahendr S. Kochar, M.D. Chief, Hypertension Section Medical College of Wisconsin 5000 West National Avenue Milwaukee, WI 53193	0	5	6	5	0	0	0	16
5221 Harold W. Schnaper, M.D. Department of Medicine Univ. of Alabama Medical Center University Station Birmingham, AL 35294	9	4	4	4	1	0	0	22

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	REJECTED IN LEAD-IN	INCLUDED			EXCLUDED			TOTAL
		NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	
5480 James W. Weeds, M.D. 338 Clinical Sciences Building 229-H University of North Carolina Chapel Hill, NC 27514	15	4	5	6	0	1	0	31
5503 Robert L. Reeves, M.D. Puget Sound Medical Investigators, Ltd. 1015 West Fourth Street Olympia, WA 98502	7	4	5	6	2	1	0	25
5564 W. Dallas Hall, M.D. Department of Medicine 69 Butler Street Atlanta, GA 30303	9	4	4	4	0	1	0	22

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	REJECTED IN LEAD-IN	INCLUDED			EXCLUDED			TOTAL
		NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	
5675 Mario A. Ragusa, M.D. 120 Bethpage Road Hicksville, NY 11801	1	4	8	5	0	0	0	18
5683 William E. Miller, M.D. Nephrology Associates, P.A. 2300 Pennsylvania Avenue Suite 4C Wilmington, DE 19806	3	7	7	6	1	0	1	25
5699 Patricia Gabow, M.D. Chief, Renal Division Department of Medicine Denver General Hospital 750 Cherokee Street Denver, CO 80204	10	3	3	4	0	0	0	20

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	REJECTED IN LEAD-IN	INCLUDED			EXCLUDED			TOTAL
		NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	NADOLOL	BENDRO-FLUMETHIAZIDE	NADOLOL AND BENDRO-FLUMETHIAZIDE	
5709 Janis L. Birchall, M.D. 1415 Third Street Corpus Christi, TX 78404	4	2	2	1	0	0	0	9
GRAND TOTALS	70	59	70	66	6	3	4	278

Table 3

REASONS FOR EXCLUSION

REASON	COMBO		BENDRO		NAD	
	n	%	n	%	n	%
PLACEBO RESPONSE (inappropriately randomized)	2	3	0	-	2	3
INSUFFICIENT DATA FOR ANALYSIS						
Treatment Failure*	0	-	0	-	2	3
Adverse Reactions	0	-	2	3	2	3
Compliance Problems	2	3	1	1	0	-
TOTAL EXCLUDED	4	6	3	4	6	9
TOTAL RANDOMIZED	70		73		65	

* Less than four weeks on active therapy.

Table 4
PRETREATMENT BLOOD PRESSURE

SYSTOLIC BP mm Hg	COMBO		BENDRO		NAD		DIASTOLIC BP mm Hg	COMBO		BENDRO		NAD	
	n	%	n	%	n	%		n	%	n	%	n	%
<150	22	33	21	30	15	25							
150-169	31	47	35	50	27	46	100-104	43	65	47	67	32	54
170-189	12	18	12	17	11	19	105-114	22	34	20	29	24	41
≥190	1	2	2	3	6	10	≥115	1	2	3	4	3	5
GEOMETRIC MEAN	156		156		161		GEOMETRIC MEAN	104		104		105	

The pretreatment blood pressures were comparable for the three groups.

The distribution of supine blood pressures (based on 195 patients) at the end of the placebo period was:

	SYSTOLIC B.P.	DIASTOLIC B.P.
Minimum:	126	100
10th Percentile:	140	100
25th Percentile:	145	100
50th Percentile:	157	102
75th Percentile:	168	108
90th Percentile:	181	110
Maximum:	224	121

Tables 4a and 4b

SEX, AGE AND WEIGHT

TREATMENT GROUP	SEX	AGE (years)				WEIGHT (kg)			
		n	FROM	TO	MEAN	n	FROM	TO	MEAN
COMBO	M	48	18	75	52.9	48	58.5	120.4	84.1
	F	17*	29	66	46.6	18	53.5	120.9	78.2
BENDRO	M	55	21	70	53.8	55	64.5	125.4	86.0
	F	15	27	69	47.9	15	53.6	120.2	82.9
NAD	M	38*	25	72	50.1	39	45.5	110.0	84.1
	F	20	27	66	49.2	19*	52.3	109.8	72.2

*Data were not reported for 1 patient.

The following table presents the racial breakdown of the three treatment groups.

RACE

TREATMENT GROUP	WHITE		BLACK		TOTAL
	n	%	n	%	
COMBO	45	66	21	32	66
BENDRO	44	63	26	37	70
NAD	40	68	19	32	59
TOTAL	129		66		195

Table 5

GEOMETRIC MEAN BLOOD PRESSURES

AT ENTRY AND LAST PLACEBO VISITS
(Based on 195 patients)

	Mean[a] Entry Visit	Mean[a] Last Placebo Visit
SUPINE		
Systolic Blood Pressure	149.3	159.2***
Diastolic Blood Pressure	98.4	105.2***
STANDING		
Systolic Blood Pressure	145.6[b]	155.8***
Diastolic Blood Pressure	100.2[b]	107.1***

[a] Geometric mean adjusted for differences among investigators.

[b] Also adjusted for missing observation.

*** Statistically significantly greater than mean at entry visit, $P<.001$.

Table 6

CHANGE IN DOSE

WEEK IN STUDY	COMBO		BENDRO		NAD	
	5 mg BENDRO 80 mg NAD	10 mg BENDRO 160 mg NAD	5 mg	10 mg	80 mg	160 mg
4	66	0	70	0	58	0
6	54	12 (18%)	32	35 (52%)	38	19 (33%)
8	54	12 (18%)	31	36 (54%)	35	20 (36%)

STATISTICAL RESULTS FOR DIASTOLIC BLOOD PRESSURE

GEOMETRIC MEAN PRE AND POST TREATMENT LEVELS AND ADJUSTED PERCENT CHANGE

	COMBO				BENDRO				NAD				STATISTICAL SIGNIFICANCE		
	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	Combo vs. Bendro	Combo vs. Nad	Bendro vs. Nad
SUPINE															
Week 4	66	103.6	87.3	-16.4%	70	103.7	94.2	-9.6%	58	104.8	91.9	-12.7%	***	*	*
Week 6	66	103.6	82.2	-17.5%	67	103.6	92.4	-11.1%	57	105.0	91.4	-13.2%	***	**	NS
Week 8	66	103.6	85.6	-17.7%	67	103.7	91.9	-11.2%	55	104.6	90.8	-13.0%	***	**	NS
STANDING															
Week 4	66	104.8	89.8	-15.1%	70	105.6	95.9	-9.2%	58	105.6	95.7	-9.9%	***	***	NS
Week 6	66	104.8	88.8	-16.2%	67	105.3	94.7	-10.3%	57	106.2	94.0	-11.7%	***	**	NS
Week 8	66	104.8	88.3	-16.1%	67	105.5	94.4	-10.1%	55	106.1	94.7	-10.3%	***	***	NS

[a] Adjusted for investigators and for differences in pretreatment levels.

* P <.05
** P <.01
*** P <.001

NS = Not significant

Table 7a

STATISTICAL RESULTS FOR SYSTOLIC BLOOD PRESSURE

GEOMETRIC MEAN PRE AND POST TREATMENT LEVELS AND ADJUSTED PERCENT CHANGE

	COMBO				BENDRO				NAD				STATISTICAL SIGNIFICANCE		
	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	Combo vs. Bendro	Combo vs. Nad	Bendro vs. Nad
SUPINE															
Week 4	66	156.2	134.9	-14.3%	70	156.0	143.1	-8.5%	58	161.9	145.4	-9.9%	***	**	NS
Week 6	66	156.2	135.2	-14.3%	67	155.5	141.3	-9.9%	57	162.3	147.0	-9.2%	**	**	NS
Week 8	66	156.2	134.6	-14.2%	67	155.8	142.5	-8.5%	55	161.3	145.3	-9.6%	***	**	NS
STANDING															
Week 4	66	155.0	130.9	-15.9%	70	154.0	139.8	-9.6%	58	157.5	145.2	-7.4%	***	***	NS
Week 6	66	155.0	131.7	-15.6%	67	153.8	138.2	-11.0%	57	157.7	143.3	-8.9%	**	***	NS
Week 8	66	155.0	131.4	-15.3%	67	153.9	140.0	-9.2%	55	156.7	144.8	-7.1%	***	***	NS

[a] Adjusted for investigators and for differences in pretreatment levels.

* P <.05
** P <.01
*** P <.001

NS = Not significant

Table 8a

INDIVIDUAL PATIENT RESPONSES

WEEK 4

TREATMENT GROUP	NORMALIZED	RESPONDERS	NONRESPONDERS	TOTALS
COMBO	44 (67%)	6 (9%)	16 (24%)	66
BENDRO	27 (39%)	5 (7%)	38 (54%)	70
NAD	21 (36%)	9 (16%)	28 (48%)	58

Table 8b

WEEK 8

TREATMENT GROUP	NORMALIZED	RESPONDERS	NONRESPONDERS	TOTALS
COMBO	54 (82%)	7 (11%)	5 (8%)	66
BENDRO	32 (48%)	9 (13%)	26 (39%)	67
NAD	29 (53%)	6 (11%)	20 (36%)	55

CHANGE IN HEART RATE

TREATMENT GROUP	n	PRE	POST	ADJ. % CHANGE
COMBO	66	76.3	65.1	-14.2
BENDRO	67	72.3	76.3	+3.3
NAD	55	74.3	62.2	-16.7

Table 9

DOSE RANGE

DAILY DOSE (mg)		SHORT-TERM TREATMENT GROUP			TOTAL
BENDRO	NAD	COMBO	BENDRO	NAD	
5	80	22	16	12	50
10	160	4	8	5	17
10	80	5	4	2	11
5	160	2	1	7	10
5	40	1	1	0	2
5	320	1	0	1	2
10	240	2	0	0	2
10	320	0	2	0	2
5	120	1	0	0	1
5	240	1	0	0	1
10	40	1	0	0	1
15	80	0	1	0	1
20	160	1	0	0	1
20	320	0	1	0	1

Table 10

CONTROL OF SUPINE BLOOD PRESSURE:
PATIENTS RECEIVING COMBINATION THERAPY
DURING SHORT-TERM

MONTH ON COMBO	n	MEAN BP END PLACEBO	MEAN BP END S-T	MEAN BP END MONTH
3	39	157/102	135/85	135/86
4	35	157/102	134/85	137/86
5	28	157/102	133/85	135/87

CONTROL OF SUPINE BLOOD PRESSURE:
PATIENTS RECEIVING SINGLE THERAPY
DURING SHORT-TERM

MONTH ON COMBO	n	MEAN BP END PLACEBO	MEAN BP END S-T	MEAN BP END MONTH
1	58	161/105	147/92	140/88
2	49	162/105	148/92	140/88
3	33	165/105	150/91	144/87

STATISTICAL RESULTS FOR HEART RATE

GEOMETRIC MEAN PRE AND POST TREATMENT LEVELS AND ADJUSTED PERCENT CHANGE

	COMBO				BENDRO				NAD				STATISTICAL SIGNIFICANCE		
	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	n	Pre Mean	Post Mean	Adjusted Change[a]	Combo vs. Bendro	Combo vs. Nad	Bendro vs. Nad
SUPINE															
Week 4	66	76.3	65.8	-12.9%	69	72.5	75.3	+2.5%	58	73.8	63.1	-15.1%	***	NS	***
Week 6	66	76.3	66.1	-13.3%	67	72.5	75.4	+1.6%	57	74.3	61.3	-18.3%	***	**	***
Week 8	66	76.3	65.1	-14.2%	67	72.3	76.3	+3.3%	55	74.3	62.2	-16.7%	***	NS	***
STANDING															
Week 4	65	82.8	68.7	-16.7%	68	77.3	81.7	+3.2%	58	80.3	65.8	-18.5%	***	NS	***
Week 6	66	82.8	68.9	-16.1%	67	77.0	80.4	+2.0%	57	80.8	65.6	-18.9%	***	NS	***
Week 8	66	82.8	69.2	-15.5%	67	77.1	81.5	+3.4%	55	80.7	65.8	-18.3%	***	NS	***

[a] Adjusted for investigators and for differences in pretreatment levels.

* P <.05
** P <.01
*** P <.001

NS = Not significant

Table 12

DRUG RELATED ADVERSE REACTIONS
SHORT TERM

ADVERSE REACTION	COMBO	BENDRO	NADOLOL
Cardiovascular			
Bradycardia	1	0	0
Cold Extremities	0	0	1
Dyspnea	0	0	3
Dyspnea Upon Exertion	0	1	0
Exercise Intolerance	0	2	0
"Heart Beats Hard"	1	0	0
Orthostatic Hypotension	1	0	1
Orthostatic Dizziness	0	2	0
Palpitations	1	0	0
CNS			
Confusion	0	1	0
Dizziness	2	1	2
Fainting	1	2	0
Headache	2	0	2
Hot Flashes	0	0	1
Lethargy/Fatigue	7	2	3
Lightheadedness	1	0	0
Listlessness	0	1	0
Nervousness	1	0	0
Paresthesia	0	0	1
Sleepiness	0	2	0
Gastrointestinal			
Constipation	3	0	0
Decrease in Appetite	1	1	0
Diarrhea	1	0	2
Excessive Salivation	0	0	1
Nausea/Vomiting	1	2	1
Genitourinary			
Decreased Libido	0	1	0
Nocturia	0	1	0
"Urinary Hesitancy at Night"	0	0	1

Table 12 (continued)

DRUG RELATED ADVERSE REACTIONS
SHORT TERM (Cont'd)

ADVERSE REACTION	COMBO	BENDRO	NADOLOL
Respiratory			
Acute Asthma	0	0	1
Miscellaneous			
Cramps	1	0	0
Dry Mouth	0	0	1
Intermittent Diaphoresis	1	0	0
Muscle Cramps	1	1	0
Scotoma	0	0	1
Weakness	1	1	0
TOTALS	28 in 15 of 70 pts. (21%)	21 in 12 of 73 pts. (16%)	22 in 12 of 65 pts. (18%)

Jean Williams
Chemist

James F. Langston
Supervisory Chemist

Constance Burner Henry
Consumer Safety Officer

Natalia A. Jorgenstern
Supervisory Consumer Safety Off.

Charles Resnick, Ph.D.
Pharmacologist

James P. Burns, Jr., Ph.D.
Supervisory Pharmacologist

Stewart Ehrreich, Ph.D.
Clinical Reviewer

Raymond Lipicky, M.D.
Acting Division Director

cc: Orig. NDA 18-647
HFN-110
HFN-110/CSO
HFN-110/RLipicky/1/4/83
sie:11/30/82-1/5/83-2/15/83-5/5/83-6/1/83:3020B

SQUIBB

J3-548C

CAUTION: Federal law prohibits dispensing without prescription.

CORZIDE® 40/5
CORZIDE® 80/5
Nadolol-Bendroflumethiazide Tablets

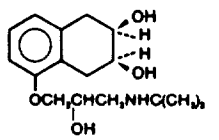
DESCRIPTION

CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration combines two antihypertensive agents: CORGARD® (nadolol), a nonselective beta-adrenergic blocking agent, and NATURETIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

Nadolol

Nadolol is a white crystalline powder. It is freely soluble in ethanol, soluble in hydrochloric acid, slightly soluble in water and in chloroform, and very slightly soluble in sodium hydroxide.

Nadolol is designated chemically as 1-(*tert*-butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol. Structural formula:

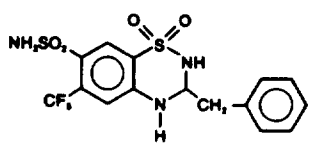


$C_{17}H_{27}NO_4$ MW 309.40 CAS-42200-33-9

Bendroflumethiazide

Bendroflumethiazide is a white crystalline powder. It is soluble in alcohol and in sodium hydroxide, and insoluble in hydrochloric acid, water, and chloroform.

Bendroflumethiazide is designated chemically as 3-benzyl-3,4-dihydro-6-(trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Structural formula:



$C_{15}H_{14}F_3N_3O_4S_2$ MW 421.41 CAS-73-48-3

J3-548C

CLINICAL PHARMACOLOGY

Nadolol

Nadolol is a nonselective beta-adrenergic receptor blocking agent. Clinical pharmacology studies have demonstrated beta-blocking activity by showing (1) reduction in heart rate and cardiac output at rest and on exercise, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Nadolol specifically competes with beta-adrenergic receptor agonists for available beta receptor sites; it inhibits both the beta$_1$ receptors located chiefly in cardiac muscle and the beta$_2$ receptors located chiefly in the bronchial and vascular musculature, inhibiting the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation proportionately. Nadolol has no intrinsic sympathomimetic activity and, unlike some other beta-adrenergic blocking agents, nadolol has little direct myocardial depressant activity and does not have an anesthetic-like membrane-stabilizing action. Animal and human studies show that nadolol slows the sinus rate and depresses AV conduction. In dogs, only minimal amounts of nadolol were detected in the brain relative to amounts in blood and other organs and tissues.

In controlled clinical studies, nadolol at doses of 40 to 320 mg/day has been shown to decrease both standing and supine blood pressure, the effect persisting for approximately 24 hours after dosing.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established; however, factors that may be involved include (1) competitive antagonism of catecholamines at peripheral (non-CNS) adrenergic neuron sites (especially cardiac) leading to decreased cardiac output, (2) a central effect leading to reduced tonic sympathetic nerve outflow to the periphery, and (3) suppression of renin secretion by blockade of the beta-adrenergic receptors responsible for renin release from the kidneys.

By blocking catecholamine-induced increases in heart rate, velocity and extent of myocardial contraction, and blood pressure, nadolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, nadolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

Although beta-adrenergic receptor blockade is useful in treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

J3-548C

Absorption of nadolol after oral dosing is variable, averaging about 30 percent. Peak serum concentrations of nadolol usually occur in three to four hours after oral administration and the presence of food in the gastrointestinal tract does not affect the rate or extent of nadolol absorption. Approximately 30 percent of the nadolol present in serum is reversibly bound to plasma protein.

Unlike many other beta-adrenergic blocking agents, nadolol is not metabolized and is excreted unchanged, principally by the kidneys.

The half-life of therapeutic doses of nadolol is about 20 to 24 hours, permitting once-daily dosage. Because nadolol is excreted predominantly in the urine, its half-life increases in renal failure (see PRECAUTIONS, *General*, and DOSAGE AND ADMINISTRATION). Steady state serum concentrations of nadolol are attained in six to nine days with once-daily dosage in persons with normal renal function. Because of variable absorption and different individual responsiveness, the proper dosage must be determined by titration.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

Bendroflumethiazide

The mechanism of action of bendroflumethiazide results in an interference with the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency. The mechanism whereby thiazides function in the control of hypertension is unknown.

INDICATIONS

CORZIDE (Nadolol-Bendroflumethiazide Tablets) is indicated in the management of hypertension.

This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS

Nadolol

Nadolol is contraindicated in bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

Bendroflumethiazide

Bendroflumethiazide is contraindicated in anuria. It is also contraindicated in patients who have previously demonstrated hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS

Nadolol

Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or nadolol should be discontinued (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Nadolol should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of nadolol can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm.

Bendroflumethiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

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

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS

General

Nadolol

Nadolol should be used with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Central Nervous System—Dizziness or fatigue has each been reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior have each been reported in approximately 6 of 1000 patients.

Respiratory—Bronchospasm has been reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS).

Gastrointestinal—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence have been reported in 1 to 5 of 1000 patients.

Miscellaneous—Each of the following has been reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision.

Sleep disturbances have been reported, but their relationship to drug usage is not clear.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with nadolol.

In addition, the following adverse reactions may occur:

Central Nervous System—Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal—Mesenteric arterial thrombosis; ischemic colitis.

Hematologic—Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Allergic—Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Miscellaneous—Reversible alopecia; Peyronie's disease; erythematous rash; arterial insufficiency.

Bendroflumethiazide

Gastrointestinal System—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), and pancreatitis.

Central Nervous System—dizziness, vertigo, paresthesia, headache, and xanthopsia.

Hematologic—leukopenia, agranulocytosis, thrombocytopenia, and aplastic anemia.

Dermatologic-Hypersensitivity—purpura, photosensitivity, rash, urticaria, and necrotizing angiitis (vasculitis, cutaneous vasculitis).

Cardiovascular—Orthostatic hypotension may occur.

Other—hyperglycemia, glycosuria, occasional metabolic acidosis in diabetic patients, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, and restlessness.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

In the event of overdosage, nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm.

In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

Treatment

Nadolol can be removed from the general circulation by hemodialysis. I determining the duration of corrective therapy, note must be taken of th long duration of the effect of nadolol. In addition to gastric lavage, th following measures should be employed, as appropriate.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It ha been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or leva terenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a beta$_2$-stimulating agent and/or theophylline derivative.

Stupor or Coma—Supportive therapy as warranted.

Gastrointestinal Effects—Symptomatic treatment as needed.

BUN and/or Serum Electrolyte Abnormalities—Institute supporti measures as required to maintain hydration, electrolyte balance, respi tion, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS). CORZIDE MA BE ADMINISTERED WITHOUT REGARD TO MEALS.

Bendroflumethiazide is usually given at a dose of 5 mg daily. The usu initial dose of nadolol is 40 mg once daily whether used alone or in comb nation with a diuretic. Bendroflumethiazide in CORZIDE is 30 percent mo bioavailable than that of 5 mg Naturetin tablets. Conversion from 5 m Naturetin to CORZIDE represents a 30 percent increase in dose of be droflumethiazide.

The initial dose of CORZIDE (Nadolol-Bendroflumethiazide Tablets) m therefore be the 40 mg/5 mg tablet once daily. When the antihypertensi response is not satisfactory, the dose may be increased by administeri the 80 mg/5 mg tablet once daily.

When necessary, another antihypertensive agent may be add gradually beginning with 50 percent of the usual recommended starti dose to avoid an excessive fall in blood pressure.

Dosage Adjustment in Renal Failure—Absorbed nadolol is excret principally by the kidneys and, although nonrenal elimination does occ dosage adjustments are necessary in patients with renal impairment. T following dose intervals are recommended:

Creatinine Clearance (ml/min/1.73 m^2)	Dosage Interval (hours)
>50	24
31-50	24-36
10-30	24-48
<10	40-60

HOW SUPPLIED

CORZIDE (Nadolol-Bendroflumethiazide Tablets)

- **40 mg nadolol combined with 5 mg bendroflumethiazide** in bottles of 1 tablets (NDC 0003-0283-50).
- **80 mg nadolol combined with 5 mg bendroflumethiazide** in bottles of 1 tablets (NDC 0003-0284-50).

Round, biconvex tablets are white to bluish white with dark bl specks. Each tablet has a full bisect bar. Tablet identification numbe 40 mg/5 mg combination, 283; 80 mg/ 5 mg combination, 284.

Storage

Keep bottle tightly closed. Store at room temperature; avoid excess heat.

E. R. Squibb & Sons, Inc.
Princeton, NJ 08540

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