

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-742

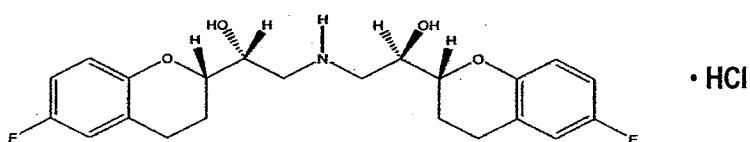
LABELING

BYSTOLIC
(nebivolol) Tablets
2.5 mg, 5 mg and 10 mg

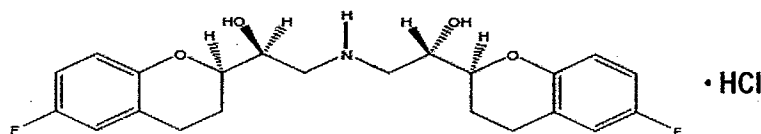
Rx only

DESCRIPTION

The chemical name for the active ingredient in BYSTOLIC (nebivolol) tablets is (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol, respectively. Nebivolol's molecular formula is (C₂₂H₂₅F₂NO₄•HCl) with the following structural formula:



SRRR – or d-nebivolol hydrochloride



RSSS – or l-nebivolol hydrochloride

MW: 441.90 g/mol

Nebivolol hydrochloride is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

BYSTOLIC as tablets for oral administration contains nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol base. In addition, BYSTOLIC contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake, FD&C Blue #2 Lake, FD&C Yellow #6 Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, polysorbate 80, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

General

Nebivolol is a β -adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 and β_2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically

relevant concentrations. At clinically relevant doses, BYSTOLIC does not demonstrate α_1 -adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β -blocking activity.

Pharmacodynamics

The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Pharmacokinetics

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β -blocking activity.

Plasma levels of d-nebivolol increase in proportion to dose in EMs and PMs for doses up to 20 mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's beta receptor affinity is > 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher C_{max} and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

Absorption and Distribution

Absorption of BYSTOLIC is similar to an oral solution. The absolute bioavailability has not been determined.

Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs.

Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. BYSTOLIC may be administered without regard to meals.

The *in vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism and Excretion

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity (see **Drug Interactions**).

After a single oral administration of ¹⁴C-nebivolol, 38% of the dose was recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Drug-Interactions

Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When BYSTOLIC is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. *In vitro* studies have demonstrated that at therapeutically relevant concentrations, d- and l-nebivolol do not inhibit any cytochrome P450 pathways.

Digoxin: Concomitant administration of BYSTOLIC (10 mg once daily) and digoxin (0.25 mg once daily) for 10 days in 14 healthy adult individuals resulted in no significant changes in the pharmacokinetics of digoxin or nebivolol (see **PRECAUTIONS, Drug Interactions**).

Warfarin: Administration of BYSTOLIC (10 mg once daily for 10 days) led to no significant changes in the pharmacokinetics of nebivolol or R- or S-warfarin following a single 10 mg dose of warfarin. Similarly, nebivolol has no significant effects on the anticoagulant activity of warfarin, as assessed by Prothrombin time and INR profiles from 0 to 144 hours after a single 10 mg warfarin dose in 12 healthy adult volunteers.

Diuretics: No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days) and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone 25 mg once daily for 10 days).

Ramipril: Concomitant administration of BYSTOLIC (10 mg once daily) and ramipril (5 mg once daily) for 10 days in 15 healthy adult volunteers produced no pharmacokinetic interactions.

Losartan: Concomitant administration of BYSTOLIC (10 mg single dose) and losartan (50 mg single dose) in 20 healthy adult volunteers did not result in pharmacokinetic interactions.

Fluoxetine: Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for d-nebivolol (see **PRECAUTIONS, Drug Interactions**).

Histamine-2 Receptor Antagonists: The pharmacokinetics of nebivolol (5 mg single dose) were not affected by the co-administration of ranitidine (150 mg twice daily). Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of d-nebivolol.

Charcoal: The pharmacokinetics of nebivolol (10 mg single dose) were not affected by repeated co-administration (4, 8, 12, 16, 22, 28, 36, and 48 hours after nebivolol administration) of activated charcoal (Actidose-Aqua[®]).

Sildenafil: The co-administration of nebivolol and sildenafil decreased AUC and C_{max} of sildenafil by 21 and 23% respectively. The effect on the C_{max} and AUC for d-nebivolol was

also small (< 20%). The effect on vital signs (e.g., pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Other Concomitant Medications: Utilizing population pharmacokinetic analyses, derived from hypertensive patients, the following drugs were observed not to have an effect on the pharmacokinetics of nebivolol: acetaminophen, acetylsalicylic acid, atorvastatin, esomeprazole, ibuprofen, levothyroxine sodium, metformin, sildenafil, simvastatin, or tocopherol.

Protein Binding: No meaningful changes in the extent of *in vitro* binding of nebivolol to human plasma proteins were noted in the presence of high concentrations of diazepam, digoxin, diphenylhydantoin, enalapril, hydrochlorothiazide, imipramine, indomethacin, propranolol, sulfamethazine, tolbutamide, or warfarin. Additionally, nebivolol did not significantly alter the protein binding of the following drugs: diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations.

Special Populations

Renal Disease: The apparent clearance of nebivolol was unchanged following a single 5 mg dose of BYSTOLIC in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). The dose of BYSTOLIC should be adjusted in patients with severe renal impairment. BYSTOLIC should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this population (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic impairment. No formal studies have been performed in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients. (see **DOSAGE AND ADMINISTRATION**).

Clinical Studies

The antihypertensive effectiveness of BYSTOLIC as monotherapy has been demonstrated in three randomized, double-blind, multi-center, placebo-controlled trials at doses ranging from 1.25 to 40 mg for 12 weeks (Studies 1, 2, and 3). A fourth placebo-controlled trial demonstrated additional antihypertensive effects of BYSTOLIC at doses ranging from 5 to 20 mg when administered concomitantly with up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) in patients with inadequate blood pressure control.

The three monotherapy trials included a total of 2016 patients (1811 BYSTOLIC, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressures (DBP) of 95 to 109 mmHg. Patients received either BYSTOLIC or placebo once daily for twelve weeks. Two of these monotherapy trials (Studies #1 and #2) studied 1716 patients in the general hypertensive population with a mean age of 54 years, 55% males, 26% non-Caucasians, 7% diabetics and 6%

genotyped as PMs. The third monotherapy trial (Study #3) studied 300 Black patients with a mean age of 51 years, 45% males, 14% diabetics, and 3% as PMs.

Placebo-subtracted blood pressure reductions by dose for each study are presented in Table 1. Most studies showed increasing response to doses above 5 mg.

Table 1. Placebo-Subtracted Least-Square Mean Reductions in Trough Sitting Systolic/Diastolic Blood Pressure (SiSBP/SiDBP mmHg) by Dose in Studies with Once Daily BYSTOLIC

	Nebivolol dose (mg)					
	1.25	2.5	5.0	10	20	30-40
Study 1	-6.6*/-5.1*	-8.5*/-5.6*	-8.1*/-5.5*	-9.2*/-6.3*	-8.7*/-6.9*	-11.7*/-8.3*
Study 2			-3.8/-3.2*	-3.1/-3.9*	-6.3*/-4.5*	
Study 3 [†]		-1.5/-2.9	-2.6/-4.9*	-6.0*/-6.1*	-7.2*/-6.1*	-6.8*/-5.5*
Study 4 [^]			-5.7*/-3.3*	-3.7*/-3.5*	-6.2*/-4.6*	

* p<0.05 based on pair-wise comparison vs placebo

[†] Study enrolled only African Americans.

[^] Study on top of one or two other antihypertensive medications.

Study #4 enrolled 669 patients with a mean age of 54 years, 55% males, 54% Caucasians, 29% Blacks, 15% Hispanics, 1% Asians, 14% diabetics, and 5% PMs. BYSTOLIC, 5 mg to 20 mg, administered once daily concomitantly with stable doses of up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) resulted in significant additional antihypertensive effects over placebo compared to baseline blood pressure.

Effectiveness was similar in subgroups analyzed by age and sex. Effectiveness was established in Blacks, but as monotherapy the magnitude of effect was somewhat less than in Caucasians.

The blood pressure lowering effect of BYSTOLIC was seen within two weeks of treatment and was maintained over the 24-hour dosing interval.

INDICATIONS AND USAGE

BYSTOLIC is indicated for the treatment of hypertension. BYSTOLIC may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

BYSTOLIC is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), or severe hepatic impairment (Child-Pugh > B), and in patients who are hypersensitive to any component of this product.

WARNINGS

Abrupt Cessation of Therapy

Patients with coronary artery disease treated with BYSTOLIC should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β -blockers. Myocardial infarction and

ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. As with other β -blockers, when discontinuation of BYSTOLIC is planned, patients should be carefully observed and advised to minimize physical activity. BYSTOLIC should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that BYSTOLIC be promptly reinstituted, at least temporarily.

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in the setting of congestive heart failure, and β -blockade may result in further depression of myocardial contractility and precipitate more severe failure. In patients who have compensated congestive heart failure, BYSTOLIC should be administered cautiously. If heart failure worsens, discontinuation of BYSTOLIC should be considered.

Angina and Acute Myocardial Infarction

BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.

Bronchospastic Diseases

In general, patients with bronchospastic diseases should not receive β -blockers.

Anesthesia and Major Surgery

If BYSTOLIC is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β -blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

The β -blocking effects of BYSTOLIC can be reversed by β -agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β -blockers.

Diabetes and Hypoglycemia

β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.

Thyrotoxicosis

β -blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β -blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease

β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Non-dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with β -blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

PRECAUTIONS

Use with CYP2D6 inhibitors

Nebivolol exposure increases with inhibition of CYP2D6 (see **Drug Interactions**). The dose of BYSTOLIC may need to be reduced.

Impaired Renal Function

BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

Impaired Hepatic Function

BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population (see **CLINICAL PHARMACOLOGY, Special Populations** and **DOSAGE AND ADMINISTRATION**).

Risk of Anaphylactic Reactions

While taking β -blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β -blocker.

Information for Patients

Patients should be advised to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, the patient should take the next scheduled dose only (without doubling it). Patients should not interrupt or discontinue BYSTOLIC without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

315 Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they
316 develop signs or symptoms of worsening congestive heart failure such as weight gain or
317 increasing shortness of breath, or excessive bradycardia.

318
319 Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral
320 hypoglycemic agents, should be cautioned that β -blockers may mask some of the manifestations
321 of hypoglycemia, particularly tachycardia. Nebivolol should be used with caution in these
322 patients.

323 324 **Drug Interactions**

325 BYSTOLIC should be used with care when myocardial depressants or inhibitors of AV
326 conduction, such as certain calcium antagonists (particularly of the phenylalkylamine
327 [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as
328 disopyramide, are used concurrently. Both digitalis glycosides and β -blockers slow
329 atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of
330 bradycardia.

331
332 BYSTOLIC should not be combined with other β -blockers. Patients receiving catecholamine-
333 depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the
334 added β -blocking action of BYSTOLIC may produce excessive reduction of sympathetic
335 activity. In patients who are receiving BYSTOLIC and clonidine, BYSTOLIC should be
336 discontinued for several days before the gradual tapering of clonidine.

337
338 **CYP2D6 Inhibitors:** Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors
339 (quinidine, propafenone, fluoxetine, paroxetine, etc.) (see **CLINICAL PHARMACOLOGY,**
340 **Drug Interactions**).

341 342 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

343 In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of
344 testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the
345 maximally recommended human dose of 40 mg on a mg/m^2 basis). Similar findings were not
346 reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum
347 recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month
348 study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6,
349 2.4, and 10 times the maximally recommended human dose). Co-administration of
350 dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia,
351 consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be
352 clinically relevant in man.

353
354 A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male
355 volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing
356 hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10
357 mg of nebivolol had no significant effect on ACTH-stimulated mean serum cortisol $\text{AUC}_{0-120 \text{ min}}$,
358 serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥ 40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats, the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, in vitro mouse lymphoma TK⁺-, in vitro human peripheral lymphocyte chromosome aberration, in vivo *Drosophila melanogaster* sex-linked recessive lethal, and in vivo mouse bone marrow micronucleus tests).

Pregnancy: Teratogenic Effects. Pregnancy Category C:

Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Labor and Delivery

Nebivolol caused prolonged gestation and dystocia at doses ≥ 5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation).

No studies of nebivolol were conducted in pregnant women. BYSTOLIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk.

Because of the potential for β -blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing.

Geriatric Use

Of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility (see Carcinogenesis, Mutagenesis and Impairment of Infertility).

ADVERSE REACTIONS

The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse events was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Adverse Reactions in Controlled Trials

Table 2 lists treatment-emergent signs and symptoms that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 2. Treatment-Emergent Adverse Events with an Incidence (over 6 weeks) \geq 1% in BYSTOLIC-treated Patients and at a Higher Frequency than Placebo-Treated Patients

	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1
Bradycardia	0	0	0	1
Dyspnea	0	0	1	1
Rash	0	0	1	1
Peripheral edema	0	1	1	1

Other Adverse Events Observed During Worldwide Clinical Trials

Listed below are other reported adverse events with an incidence of at least 1% in the more than 5300 patients treated with BYSTOLIC in controlled or open-label trials, whether or not

attributed to treatment, except for those already appearing in Table 2, terms too general to be informative, minor symptoms, or events unlikely to be attributable to drug because they are common in the population. These adverse events were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a whole: asthenia.

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia and hyperuricemia

Nervous System Disorders: paraesthesia

Laboratory

In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

Events Identified from Spontaneous Reports of BYSTOLIC Received Worldwide.

The following adverse events have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse events have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Events common in the population have generally been omitted. Because these events were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/ Claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

OVERDOSAGE

In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdose are bradycardia and hypotension. Other important adverse events reported with BYSTOLIC overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β -blocker overdose include bronchospasm and heart block.

The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhidrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β -blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypotension: Administer IV fluids and vasopressors. Intravenous glucagon may be useful.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure: Initiate therapy with a digitalis glycoside and diuretics. In certain cases, consideration should be given to the use of inotropic and vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β_2 -agonist and/or aminophylline.

Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 13-hour half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

Call the National Poison Control Center (800-222-1222) for the most current information on β -blocker overdose treatment.

DOSAGE AND ADMINISTRATION

The dose of BYSTOLIC should be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment

In patients with severe renal impairment (CrCl less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; upward titration should be performed cautiously if needed.

BYSTOLIC has not been studied in patients receiving dialysis (see **CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment

In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once-daily; upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population (see **PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Special Populations**).

Geriatric Patients

It is not necessary to adjust the dose in the elderly (see above and **PRECAUTIONS, Geriatric Use**).

CYP2D6 Polymorphism (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**)

No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

HOW SUPPLIED

BYSTOLIC is available as tablets for oral administration containing nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol.

BYSTOLIC tablets are triangular-shaped, biconvex, unscored, differentiated by color and are engraved with "FL" on one side and the number of mg (2 ½, 5, or 10) on the other side. BYSTOLIC tablets are supplied in the following strengths and package configurations:

BYSTOLIC			
Tablet Strength	Package Configuration	NDC #	Tablet Color
2.5 mg	Bottle of 30	0456-1402-30	Light Blue
	Bottle of 100	0456-1402-01	
5 mg	Bottle of 30	0456-1405-30	Beige
	Bottle of 100	0456-1405-01	
	10 x 10 Unit Dose	0456-1405-63	
10 mg	Bottle of 30	0456-1410-30	Pinkish -Purple
	Bottle of 100	0456-1410-01	
	10 x 10 Unit Dose	0456-1410-63	

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Forest Pharmaceuticals Inc.
A Division of Forest Laboratories
St. Louis, MO

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/s/

Robert Temple
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