PRODUCT MONOGRAPH

PrBYSTOLIC®

Nebivolol Tablets

2.5 mg, 5 mg, 10 mg, and 20 mg Nebivolol
(as nebivolol hydrochloride)

Antihypertensive Agent

Forest Laboratories Canada Inc.
500 - 85 Enterprise Blvd.
Markham, Ontario
L6G 0B5
www.allergan.ca

Date of Preparation:
December 19, 2012

Date of Revision:
June 16, 2016

Submission Control No: 190670

Table of Contents

[Pr]BYSTOLIC®
Nebivolol Tablets

(as nebivolol hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet 2.5 mg, 5 mg, 10 mg, 20 mg	Colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake (10 and 20 mg only), 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

INDICATIONS AND CLINICAL USE

BYSTOLIC (nebivolol tablets) is indicated for the treatment of mild to moderate essential hypertension.

BYSTOLIC may be used alone or concomitantly with thiazide diuretics or angiotensin converting enzyme (ACE) inhibitors [see DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION and CLINICAL TRIALS].

BYSTOLIC is not recommended for the emergency treatment of hypertensive crises.

Geriatrics (≥ 65 years of age):
No dosage adjustment is required in geriatric patients. Of the total number of patients receiving BYSTOLIC in clinical studies, 436 (18%) were 65 years of age or older. No differences in efficacy or safety of BYSTOLIC were observed between older and younger patients [see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Pediatrics (< 18 years of age):
The safety and efficacy of BYSTOLIC in pediatric patients have not been established and therefore use in children is not recommended.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Severe bradycardia (generally <50 bpm prior to start of therapy)
- Patients with cardiogenic shock
- Decompensated heart failure
- Second or third degree atrioventricular (AV) block
- Sick sinus syndrome or sinoatrial block
- Patients with severe hepatic impairment (Child-Pugh Score >B)
- Severe peripheral arterial circulatory disorders
- Patients with the rare hereditary conditions of Galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

WARNINGS AND PRECAUTIONS

General

Effects on ability to drive and use machines

No studies on the effects of BYSTOLIC (nebivolol tablets) on the ability to drive and use machines have been performed. Some adverse effects of a reduction in blood pressure, such as lightheadedness, dizziness or syncope may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance.

Use with CYP2D6 Inhibitor

Nebivolol exposure increases significantly with inhibition of CYP2D6 [see DRUG INTERACTIONS]. The dose of BYSTOLIC may need to be reduced.

Cardiovascular

Abrupt Cessation of Therapy

Do not abruptly discontinue BYSTOLIC therapy in patients with coronary artery disease. Severe exacerbation of angina, 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 angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed and advised to limit physical activity to a minimum. The same frequency of administration should be maintained. In situations of greater urgency, BYSTOLIC should be discontinued stepwise over a shorter time and under closer observation.

If the angina worsens or acute coronary insufficiency develops, re-start BYSTOLIC promptly, at

least temporarily.

Decreased Heart Rate and PR Interval Prolongation
Like other β_1-blocking agents, BYSTOLIC causes a decrease in heart rate and PR interval prolongation [see ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography]. Bradycardia and atrioventricular block have been reported with the use of BYSTOLIC [see ADVERSE REACTIONS]. Caution should be observed in patients with first degree atrioventricular block, conduction disorders, a history of syncope or arrhythmia, angina, or ischemic heart disease. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk [see DRUG INTERACTIONS].

Sinus Bradycardia
Severe sinus bradycardia may occur with the use of BYSTOLIC from unopposed vagal activity remaining after blockade of β_1-adrenergic receptors; in such cases, dosage should be reduced.

Peripheral Artery Disorders
β-blockers may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to their blood pressure lowering effect. Caution should be exercised in individuals with such disorders.

Non-dihydropyridine Calcium Channel Blockers
The combination of non-dihydropyridine calcium channel blockers of the verapamil and diltiazem type and β-blockers warrants caution since additive effects on myocardial contractility, heart rate and AV conduction have been observed. Close medical supervision is recommended [see DRUG INTERACTIONS].

Endocrine and Metabolism
Diabetes and Hypoglycemia
BYSTOLIC should be used with caution in patients subject to hypoglycemic episodes since 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. BYSTOLIC is β_1-selective; however, it is not known whether BYSTOLIC has these effects. Patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents should be advised about these possibilities.

Thyrotoxicosis
In patients with thyrotoxicosis, possible deleterious effects from long-term use of BYSTOLIC have not been adequately appraised. β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia and give a false impression of improvement. Therefore, these patients should be carefully monitored for thyroid function. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Pheochromocytoma
BYSTOLIC should be used with caution and only after pretreatment with α-receptor blockers in patients with known or suspected pheochromocytoma.

Hepatic/Biliary/Pancreatic
Impaired Hepatic Function
Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic impairment [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Immune
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 accidental, diagnostic, or therapeutic challenge. There may be increased difficulty in treating an allergic-type reaction in patients on β-blockers since these patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. While larger doses of epinephrine may be needed to overcome the bronchospasm, these doses can be associated with excessive α-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm.

Peri-Operative Considerations
Anesthesia and Major Surgery
It is not advisable to withdraw β-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using BYSTOLIC with anesthetic agents that depress the myocardial function, such as ether, cyclopropane, and trichloroethylene [see DRUG INTERACTIONS]. Some patients receiving β-adrenoceptor blocking drugs have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has been reported.

In emergency surgery, the β-blocking effects of BYSTOLIC can be reversed by β-agonists, *e.g.*, dobutamine or isoproterenol.

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.

Renal
Impaired Renal Function
Renal clearance of nebivolol is decreased in patients with severe renal impairment. BYSTOLIC has not been studied in patients receiving dialysis and is therefore not recommended for use in this patient population [see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Respiratory

Bronchospastic Disease

In general, patients with bronchospastic pulmonary disease should not receive β-blockers. However, because of its relative β_1-selectivity, BYSTOLIC may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since β_1-selectivity is not absolute, the lowest possible dose of BYSTOLIC should be employed, a β_2-agonist (bronchodilator) should be made available, and the patient should be monitored closely. In patients already on bronchodilator therapy the dose may have to be increased.

Skin

Oculomucocutaneous Syndrome

Various skin rashes and conjunctival xerosis have been reported with β-blockers, including BYSTOLIC. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one β-adrenergic blocking agent (practolol). This syndrome has not been observed with BYSTOLIC. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Special Populations

Pregnant Women: No studies of nebivolol were conducted in pregnant women. Use BYSTOLIC during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus, taking into account that toxicity was seen in animals.

Animal Data: In rats, maternal toxicity included mortality, ptosis and decreased body weights at ≥10 mg/kg (~5 times the maximum recommended human dose (MRHD) on body surface area basis). Reprotoxicity included low prolonged gestation with dystocia, increased duration of gestation and decreased nursing behaviour at doses ≥5 mg/kg (~2.5 times the MRHD on body surface area basis). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate.

Nebivolol or its metabolites crossed the placental barrier in pregnant rats. When nebivolol was administered to pregnant rats, developmental abnormalities including split thoracic vertebrae changes in sternebrae and ureter dilatation occurred at 40 mg/kg (~20 times the MRHD on body surface area basis).

Nursing Women: It is not known whether this drug is excreted in human milk, but nebivolol and its metabolites have been found in the milk of lactating rats. Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended in nursing women. A decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the nursing mother.

Pediatrics (< 18 years of age): Safety and efficacy in pediatric patients have not been established and therefore use in children is not recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

BYSTOLIC (nebivolol tablets) has been evaluated for safety in more than 7,100 patients with hypertension with a clinical trial exposure to BYSTOLIC in approximately 5,400 patients. Patients received BYSTOLIC for up to 36 months, with over 1,000 patients treated for at least 6 months, and approximately 500 patients for more than one year.

In placebo-controlled monotherapy trials, the most common adverse events (≥ 2% of patients) observed with BYSTOLIC were headache (7.1%), fatigue (3.6%), nasopharyngitis (3.1%), dizziness (2.9%), diarrhea (2.5%), and upper respiratory tract infections (2.1%). BYSTOLIC was well tolerated and adverse events have generally been mild to moderate in intensity.

In placebo-controlled monotherapy trials, discontinuation of therapy due to adverse events was reported in 2.6% of patients treated with BYSTOLIC (47/1811), and in 2.0% of patients given placebo (4/205). The most common events leading to discontinuation are headache (0.2%), nausea (0.2%), bradycardia (0.2%), myocardial infarction (0.2%), orthostatic hypotension (0.1%), dyspnea (0.1%), and chest pain (0.1%) for patients who received BYSTOLIC.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In three multi-center, randomized, parallel-group, double-blind, placebo-controlled monotherapy trials, 1,811 hypertensive patients were treated over 12 weeks with a BYSTOLIC dose ranging from 1.25 mg to 40 mg, and 205 patients were given placebo. The median exposure to treatment in these three trials was 85-days.

Table 1: Number (%) of Patients with Adverse Events (Incidence ≥1% in any BYSTOLIC group) by Preferred Term - Placebo-Controlled, 12-Week Monotherapy Studies (Pooled Safety Population)

System Organ Class/ Preferred Term	Placebo (n=205)	BYSTOLIC 2.5 mg (n=131)	BYSTOLIC 5 mg (n=459)	BYSTOLIC 10 mg (n=461)	BYSTOLIC 20 mg (n=460)
Cardiac Disorders					

System Organ Class/ Preferred Term	Placebo (n=205)	BYSTOLIC 2.5 mg (n=131)	BYSTOLIC 5 mg (n=459)	BYSTOLIC 10 mg (n=461)	BYSTOLIC 20 mg (n=460)
Bradycardia/Sinus Bradycardia	1 (0.5%)	0	3 (0.7%)	3 (0.7%)	10 (2.2%)
Palpitations	0	2 (1.5%)	2 (0.4%)	4 (0.9%)	1 (0.2%)
Eye Disorders					
Vision blurred	0	2 (1.5%)	2 (0.4%)	3 (0.7%)	3 (0.7%)
Gastrointestinal Disorders					
Diarrhea	4 (2.0%)	2 (1.5%)	11 (2.4%)	9 (2.0%)	15 (3.3%)
Nausea	1 (0.5%)	3 (2.3%)	3 (0.7%)	13 (2.8%)	10 (2.2%)
Constipation	5 (2.4%)	1 (0.8%)	2 (0.4%)	5 (1.1%)	3 (0.7%)
Dry mouth	0	2 (1.5%)	3 (0.7%)	3 (0.7%)	1 (0.2%)
Dyspepsia	3 (1.5%)	1 (0.8%)	5 (1.1%)	5 (1.1%)	4 (0.9%)
General Disorders and Administration Site Conditions					
Fatigue	3 (1.5%)	6 (4.6%)	10 (2.2%)	11 (2.4%)	27 (5.9%)
Chest Pain	0	2 (1.5%)	2 (0.4%)	5 (1.1%)	8 (1.7%)
Edema	0	2 (1.5%)	0	0	1 (0.2%)
Edema Peripheral	1 (0.5%)	1 (0.8%)	4 (0.9%)	6 (1.3%)	2 (0.4%)
Pain	0	0	1 (0.2%)	1 (0.2%)	5 (1.1%)
Infections and Infestations					
Nasopharyngitis	9 (4.4%)	5 (3.8%)	17 (3.7%)	10 (2.2%)	17 (3.7%)
Upper Respiratory Tract Infection	5 (2.4%)	2 (1.5%)	11 (2.4%)	6 (1.3%)	12 (2.6%)
Urinary Tract Infection	2 (1.0%)	2 (1.5%)	9 (2.0%)	2 (0.4%)	7 (1.5%)
Sinusitis	2 (1.0%)	0	6 (1.3%)	7 (1.5%)	5 (1.1%)
Influenza	1 (0.5%)	0	6 (1.3%)	2 (0.4%)	6 (1.3%)
Bronchitis	1 (0.5%)	0	4 (0.9%)	4 (0.9%)	5 (1.1%)
Investigations					
C-Reactive Protein Increased	1 (0.5%)	5 (3.8%)	3 (0.7%)	4 (0.9%)	5 (1.1%)
Blood Triglycerides Increased	3 (1.5%)	1 (0.8%)	1 (0.2%)	9 (2.0%)	3 (0.7%)
Low Density Lipoprotein Increased	1 (0.5%)	2 (1.5%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	3 (1.5%)	3 (2.3%)	6 (1.3%)	7 (1.5%)	4 (0.9%)
Back Pain	2 (1.0%)	1 (0.8%)	2 (0.4%)	7 (1.5%)	9 (2.0%)
Pain In Limb	1 (0.5%)	1 (0.8%)	5 (1.1%)	2 (0.4%)	3 (0.7%)
Nervous System Disorders					
Headache	12 (5.9%)	8 (6.1%)	41 (8.9%)	28 (6.1%)	28 (6.1%)
Dizziness	4 (2.0%)	4 (3.1%)	7 (1.5%)	12 (2.6%)	19 (4.1%)
Carpal Tunnel Syndrome	0	2 (1.5%)	0	0	0
Psychiatric Disorders					
Insomnia	1 (0.5%)	3 (2.3%)	3 (0.7%)	4 (0.9%)	9 (2.0%)

System Organ Class/ Preferred Term	Placebo (n=205)	BYSTOLIC 2.5 mg (n=131)	BYSTOLIC 5 mg (n=459)	BYSTOLIC 10 mg (n=461)	BYSTOLIC 20 mg (n=460)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	2 (1.0%)	3 (2.3%)	5 (1.1%)	7 (1.5%)	3 (0.7%)
Sinus Congestion	0	3 (2.3%)	4 (0.9%)	4 (0.9%)	1 (0.2%)
Dyspnea	1 (0.5%)	0	1 (0.2%)	5 (1.1%)	7 (1.5%)
Pharyngolaryngeal Pain	0	1 (0.8%)	1 (0.2%)	3 (0.7%)	5 (1.1%)
Skin and Subcutaneous Tissue Disorders					
Rash	0	3 (2.3%)	0	5 (1.1%)	4 (0.9%)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events reported in the placebo-controlled studies with incidence rates of less than <1% and at a higher frequency than placebo-treated patients are listed below.

Blood and Lymphatic System Disorders: anemia; leukopenia; lymphadenopathy

Cardiac Disorders: myocardial infarction; myocardial ischemia; angina pectoris; atrioventricular block first degree; cardiac failure congestive; extrasystoles; tachycardia; withdrawal arrhythmia

Ear And Labyrinth Disorders: deafness; ear pain; hearing impaired; vertigo

Eye Disorders: conjunctival haemorrhage; conjunctivitis; eye pain; glaucoma; vision disturbances

Gastrointestinal Disorders: abdominal pain; flatulence; gastro-oesophageal reflux disease; oral mucosal lesions; toothache; vomiting

General Disorders and Administration Site Conditions: influenza-like illness; pyrexia; weakness

Immune System Disorders: hypersensitivity

Infections and Infestations: fungal infection; gastroenteritis; hepatitis; localized infection; lower respiratory tract infection

Investigations: alanine aminotransferase increased; aspartate aminotransferase increased; blood alkaline phosphatase increased; blood glucose increased; blood uric acid increased; cardiac murmur; haematocrit/hemoglobin decreased; high density lipoprotein decreased; weight increased

Metabolism and Nutrition Disorders: diabetes mellitus; gout; hypercholesterolaemia; hyperkalaemia; hyperlipidaemia

Musculoskeletal and Connective Tissue Disorders: arthritis; muscle cramps; muscle weakness; myalgia

Nervous System Disorders: burning sensation; cerebral haemorrhage; hypoaesthesia; memory impairment; migraines; paraesthesia; transient ischemic attack

Psychiatric Disorders: anxiety; decreased libido; depression; nightmare

Renal and Urinary Disorders: haematuria; proteinuria; urinary frequency increased

Reproductive System and Breast Disorders: dysmenorrhoea; erectile dysfunction; galactorrhoea

Respiratory, Thoracic and Mediastinal Disorders: epistaxis; nasal congestion

Skin and Subcutaneous Tissue Disorders: angioneurotic oedema; contusion; pruritus; sweating

Vascular Disorders: deep vein thrombosis; flushing; hypotension; intermittent claudication; orthostatic hypotension; phlebitis

Abnormal Hematologic and Clinical Chemistry Findings

In placebo-controlled monotherapy studies, patients were reported to have laboratory abnormalities of clinical significance for the clinical laboratory parameters shown in Table 2.

Table 2: Number of Patients with Abnormal Laboratory Results of Clinical Significance Occurring After First Dose of Treatment in Placebo-Controlled, 12-Week Monotherapy Studies (Pooled Safety Population)

Parameters (values of clinical significance)	Placebo (n=205)	Nebivolol			
		2.5 mg (n=131)	5 mg (n=459)	10 mg (n=461)	20 mg (n=460)
Chemistry					
AST (≥3 X ULN)	0	0	3 (0.7%)	2 (0.4%)	4 (0.9%)
Blood urea nitrogen (BUN) (≥10.7 mmol/L)	0	1 (0.8%)	2 (0.4%)	3 (0.7%)	2 (0.4%)
Uric acid (Male≥625 µmol/L; Female ≥506 µmol/L)	0	0	2 (0.4%)	0	1 (0.2%)
Hematology					
Eosinophils (≥10%)	2 (1.0%)	1 (0.8%)	8 (1.7%)	3 (0.7%)	5 (1.1%)
Hematocrit (Male≤37%; Female≤32%)	3 (1.5%)	2 (1.5%)	4 (0.9%)	5 (1.1%)	9 (2.0%)
Hemoglobin (Male≤7.1 mmol/L; Female≤5.9 mmol/L)	1 (0.5%)	1 (0.8%)	2 (0.4%)	1 (0.2%)	4 (0.9%)
Urinalysis					
Protein (increase≥2units)	2 (1.0%)	0	4 (0.9%)	1 (0.2%)	5 (1.1%)

AST, aspartate aminotransferase; **Normal ranges:** AST: 0-42 U/L; BUN: 2.5-8.9 mmol/L; uric acid: 149-446 µmol/L; hematocrit: 35-46%; hemoglobin: 7.4-9.7 mmol/L.

The clinical laboratory parameters for which patients were reported to experience shifts from normal at baseline to the out-of-normal range during nebivolol treatment phase with a higher frequency than in placebo-treated patients are listed below.

Triglycerides: Shifts from normal to values above the upper limit of normal (2.2 mmol/L) were reported in 11.5%, 14.3%, 17.0% and 16.3% of patients treated with nebivolol 2.5 mg, 5 mg, 10 mg and 20 mg, respectively, as compared to 10.5% with placebo.

HDL cholesterol: Shifts from normal to values below the lower limit of normal (0.9 mmol/L) were reported in 1.1%, 3.0%, 4.4% and 4.1% of patients treated with nebivolol 2.5 mg, 5 mg, 10 mg and 20 mg, respectively, as compared to 1.3% with placebo.

Post-Market Adverse Drug Reactions

Other adverse events reported in post-marketing use include: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, angioedema, atrioventricular block (both second and third degree), bronchospasm, hepatitis, hypersensitivity (including urticaria and allergic vasculitis), peripheral ischemia/claudication, pruritus, psoriasis, Raynaud's phenomenon, somnolence, suicidal ideation, syncope,

thrombocytopenia and various rash and skin disorders. Few cases, some fatal, of cardiac arrest have been reported shortly after initiation of nebivolol therapy; causality has not been established.

DRUG INTERACTIONS

Overview

Nebivolol is a substrate for CYP2D6. Inhibitors, inducers or substrates of CYP2D6 alter the exposure of nebivolol. When BYSTOLIC (nebivolol tablets) is co-administered with an inhibitor, inducer, or substrate of this enzyme, the dose of BYSTOLIC may need to be adjusted.

Based on *in vitro* results, the potential of nebivolol to have a clinically meaningful inhibitory effect on other cytochrome P450 isozymes is unlikely (i.e. CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4/5 and CYP4A9/11) [see DETAILED PHARMACOLOGY].

Like other β_1-blocking agents, BYSTOLIC causes a decrease in heart rate and PR interval prolongation [see WARNINGS AND PRECAUTIONS, Cardiovascular and ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography]. The concomitant use of BYSTOLIC with other drugs that lower heart rate and/or prolong the PR interval, including, but not limited to, antiarrhythmics, non-dihydropyridine calcium channel blockers, digitalis glycosides, α_2-adrenoceptor agonists, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators (*e.g.* fingolimod), and some of the HIV protease inhibitors, should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk.

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions

Common Name	Reference	Effect	Clinical Comments
α_2-adrenergic receptor agonists (*e.g.*, clonidine, guanethidine)	T	The added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity.	Closely monitor patients concomitantly treated with an α_2-agonist. In patients who are receiving BYSTOLIC and clonidine, discontinue BYSTOLIC for several days before the gradual tapering of clonidine.
Angiotensin converting enzyme (ACE) inhibitors	CT	No pharmacokinetic interaction was seen when nebivolol was co-administered with ramipril. The risk of bradycardia/sinus bradycardia was slightly increased when nebivolol was given concomitantly with lisinopril compared to administration of nebivolol alone. More patients showed a shift in total	Use caution when BYSTOLIC is co-administered with ACE inhibitors.

Common Name	Reference	Effect	Clinical Comments
		cholesterol and low density lipoprotein cholesterol (LDL-C) from normal to high range when treated concomitantly with nebivolol and lisinopril compared to patients treated with each of these drugs alone.	
Anesthetic agents (*e.g.*, ether, cyclopropane and trichloroethylene)	T	Concomitant use with anesthetic agents which depress myocardial function can exacerbate myocardial depression.	Monitor patients ECG and blood pressure closely when BYSTOLIC is co-administered with anesthetic agents.
Antiarrhythmics (*e.g.*, amiodarone, disopyramide, flecainide)	C, T	BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of atrioventricular conduction.	Monitor patients closely when BYSTOLIC is co-administered with antiarrhythmics. Dose adjustment may be needed.
Antidiabetic agents (*e.g.*, insulin and oral hypoglycemic agents)	C, T	β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.	Use caution when BYSTOLIC is co-administered in patients subject to hypoglycemic episodes.
Calcium channel blockers (particularly verapamil and diltiazem, etc.)	C*, T	BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of atrioventricular conduction. Cases of serious effects (e.g. bradycardia, syncope, requiring hospitalization) in patients treated with nebivolol and verapamil, diltiazem were reported.	Monitor patients closely when BYSTOLIC is co-administered with non-dihydropyridine calcium channel blockers.
CYP2D6 inducers (*e.g.*, dexamethasone, rifampin)	T	Inducers of CYP2D6 may decrease the exposure of nebivolol.	The dose of BYSTOLIC may need to be adjusted.
CYP2D6 inhibitors (*e.g.*, fluoxetine, quinidine, paroxetine, propafenone and cimetidine) and substrates (*e.g.*, thioridazine, venlafaxine)	CT, C	Inhibitors or substrates of CYP2D6 increase the exposure of nebivolol. Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of BYSTOLIC to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for *d*-nebivolol.	Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors/substrates. The dose of BYSTOLIC may need to be reduced.
Digoxin	T, C*	Concomitant administration of BYSTOLIC and digoxin can exacerbate slowing atrioventricular conduction and heart rate. Cases of bradycardia were reported with concomitant use.	Monitor patients closely when BYSTOLIC is co-administered with digoxin.

Common Name	Reference	Effect	Clinical Comments
Diuretics: hydrochlorothiazide, furosemide, spironolactone	CT, C*	No pharmacokinetic interactions were observed in healthy adults between BYSTOLIC (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). Cases of bradycardia, hypotension and loss of consciousness were reported with concomitant use.	Use caution when BYSTOLIC is co-administered with diuretics.
Fingolimod	CT	Bradycardia	Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment administration e.g., at least overnight monitoring, is recommended.
Histamine-2 Receptor Antagonists	CT	The pharmacokinetics of BYSTOLIC (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.	No specific action required.
Sildenafil	CT	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%). Given that both agents modulate the nitric oxide pathway, vital signs were measured.	Use caution when BYSTOLIC is co-administered with sildenafil. When co-administered, the effects on pulse and blood pressure were approximately the sum of the effects of sildenafil and nebivolol.
Valsartan	CT	Concomitant administration of BYSTOLIC (20 mg once daily) and valsartan (320 mg once daily) in 30 healthy adult volunteers resulted in a 47% and 19% reduction in *d*-nebivolol C_{max} and AUC, respectively.	

C=Case Study, CT=Clinical Trial, I=*In vitro*, T=Theoretical, C* = Case Report from PSUR data

No pharmacokinetic interaction has been observed when nebivolol is concomitantly administered with activated charcoal, alcohol, digoxin, losartan or warfarin in healthy adult volunteers. Moreover, nebivolol has no significant effects on the anticoagulant activity of warfarin (prothrombin time and INR).

Drug-Food Interactions

Food does not significantly alter the pharmacokinetics of nebivolol. BYSTOLIC may be taken with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory testing have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
In the treatment of mild to moderate essential hypertension, the dose of BYSTOLIC (nebivolol tablets) 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. For patients requiring further reduction in blood pressure, the dose can be increased at two-week intervals up to 20 mg once daily.

Once-daily dosing has shown to sustain efficacy over 24 hours. A more frequent dosing regimen is unlikely to be beneficial.

Concomitant use of ACE inhibitors
When BYSTOLIC is to be co-administered with an ACE inhibitor, the lowest dose of the added agent should be employed initially and if needed, can be then increased at two-week intervals up to the maximum recommended dose [see DRUG INTERACTIONS].

Renal Impairment
In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients receiving dialysis and is therefore not recommended for use in this patient population [see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Hepatic Impairment
In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore is contraindicated in that population [see CONTRAINDICATIONS, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Geriatric Patients
No dose adjustments are usually necessary for elderly patients.

CYP2D6 Polymorphism
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 [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Missed Dose
If patients miss a dose, they should wait until their next scheduled dose. Patients should not double their dose. BYSTOLIC should be taken once approximately every 24 hours.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms:
In clinical trials and worldwide post-marketing experience there were reports of BYSTOLIC (nebivolol tablets) overdose. The most common signs and symptoms associated with BYSTOLIC overdosage are bradycardia and hypotension. Other important adverse reactions reported with BYSTOLIC overdose include heart failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions 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 hyperhydrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Treatment:
Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. Administration of activated charcoal is not recommended as it has no effect on the pharmacokinetics of BYSTOLIC.

If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β-blockers, consider the following general measures, including stopping BYSTOLIC, 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): Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases,

consider 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.

Supportive measures should continue until clinical stability is achieved.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BYSTOLIC (nebivolol tablets) is a cardioselective β-adrenergic receptor antagonist with vasodilating activity. The exact mechanism of action of its antihypertensive response has not been definitively established. The ability of β-adrenergic receptor antagonists to decrease blood pressure appears to be related to decreased heart rate, decreased myocardial contractility, decreased sympathetic activity, and suppression of renin activity. Nebivolol also has vasodilating properties, likely due to its ability to increase nitric oxide release from human endothelial cells, which may decrease peripheral vascular resistance, but their relative contribution to the overall blood pressure lowering effect of nebivolol has not been demonstrated.

Nebivolol lacks appreciable affinity for α-adrenergic receptors. Nebivolol does not appear to have intrinsic sympathomimetic activity at β_1-adrenergic receptors.

Pharmacodynamics

Nebivolol is preferentially β_1-selective with a 320-fold higher affinity for human cardiac β_1- vs. β_2-adrenergic receptors. In extensive metabolizers (most of the population) and at doses less than or equal to 20 mg, nebivolol is preferentially β_1-selective. At clinically relevant doses in extensive metabolizers, nebivolol is not expected to significantly block α_1-adrenergic receptors as determined in a clinical study with the 5 mg dose and inferred from nebivolol C_{max} (32 nM at 20 mg dose) in relation to its binding affinity for α_1-adrenergic receptors (K_i of 330 nM). In poor metabolizers and at higher doses, nebivolol inhibits both β_1- and β_2-adrenergic receptors. Several metabolites of nebivolol that demonstrate binding affinity at the β_1-adrenergic receptor have been identified following oral administration of nebivolol. The K_i for the active metabolites range from 0.7 nM to 19.8 nM, compared to K_i = 0.7 nM for nebivolol, suggesting that these metabolites may contribute to the β-blocking activity.

Nebivolol is a racemic mixture of *d*-nebivolol and *l*-nebivolol. Exposure to *l*-nebivolol is higher than to *d*-nebivolol but *l*-nebivolol contributes little to the drug's β_1-blocking activity as *d*-nebivolol's β-receptor affinity is > 1000-fold higher than *l*-nebivolol [see DETAILED PHARMACOLOGY].

Electrocardiography: A randomized, open-label, placebo- and active-controlled (atenolol and moxifloxacin), parallel group study was performed to assess the effect of BYSTOLIC on electrocardiographic intervals in healthy subjects (N=67-71/group). BYSTOLIC was administered at a therapeutic dose of 20 mg QD on days 1-3 and a supratherapeutic dose of 40 mg QD on days 4-7. ECG assessments were performed on days 1, 4, and 7. BYSTOLIC reduced heart rate and increased the PR interval as presented in Table 4.

Table 4: Maximum Placebo-Adjusted Mean Changes from Baseline During Treatment with BYSTOLIC on Days 1, 4, and 7

	Heart Rate (bpm)		PR Interval (msec)	
	Mean (90% CI)	Time (h)	Mean (90% CI)	Time (h)
Day 1	-14.2 (-18.0, -10.3)	6	13.0 (9.0, 17.0)	2.5
Day 4	-19.4 (-23.1, -15.7)	4	13.8 (9.3, 18.3)	2.5
Day 7	-20.8 (-24.2, -17.4)	23.5	11.4 (7.2, 15.5)	4.0

Similar effects on heart rate and the PR interval were seen with the active comparator atenolol, administered as 100 mg QD on days 1-3 and as 200 mg QD on days 4-7.

BYSTOLIC was not demonstrated to have a treatment-related effect on the Fridericia-corrected QT interval ($QTcF=QT/RR^{0.33}$) in this study.

Pharmacokinetics

Table 5: Summary of *d,l*-Nebivolol Pharmacokinetic Parameters after Repeated Oral Administration of 10 mg Dose for 14 Days

Parameter	Extensive Metabolizers (EM)	Poor Metabolizers (PM)
AUC (ng.hr/ml)	19.7	663
Cmax (ng/ml)	3.5	32
Tmax (hr)	1.2	3.7
$T_{1/2}$ (hr)	12.7	56
CL/F (L/hr)	657	16

Absorption: BYSTOLIC is an immediate release tablet. The absolute bioavailability has not been determined. Pharmacokinetic steady state is reached in 3 and 5 days in CYP2D6 extensive and poor metabolizers, respectively.

Food does not significantly alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. BYSTOLIC may be administered with or without food.

Distribution: In human plasma, approximately 98% of nebivolol is bound to protein (mostly to albumin), regardless of nebivolol concentration, and the drug is widely distributed into tissues, including the brain.

Metabolism: Nebivolol is predominantly (75%) metabolized by cytochrome P450 2D6 via direct glucuronidation and to a lesser extent, via N-dealkylation and oxidation of the parent

compound. Its stereospecific metabolites contribute to the pharmacologic activity. Nebivolol is also metabolized to a lesser extent by CYP3A4/5 (16-20%). *d*-Nebivolol, has an effective half-life of about 13 hours in CYP2D6 extensive metabolizers (EM, most people), and 22 hours in poor metabolizers (PM) and exposure to *d*-nebivolol is substantially increased in poor metabolizers. This may have less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), partially contribute to β-blocking activity of nebivolol.

Excretion: After a single oral administration of ^{14}C-nebivolol, 37% of the dose was recovered in urine and 42% in feces for EMs and 57% in urine and 8% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of nebivolol in patients <18 years of age has not been studied.

Geriatrics: Based on the results of a population pharmacokinetic analysis, no differences were seen in the pharmacokinetics of nebivolol in elderly (≥ 65 years) patients as compared to younger patients.

Gender: Based on the results of a population pharmacokinetic analysis, no differences in the pharmacokinetics of nebivolol were seen between males and females.

Race: Based on the results of a population pharmacokinetic analysis, no differences were observed in the pharmacokinetics of nebivolol and its glucuronide metabolites among different races.

Hepatic Insufficiency: *d*-Nebivolol peak plasma concentration and exposure (AUC) increased 3.5-fold, and the apparent clearance decreased by 90% in patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been performed in patients with severe hepatic impairment and nebivolol is contraindicated in these patients.

Renal Insufficiency: The exposure (AUC) of *d*-nebivolol increased approximately 2- and 5-fold in patients with moderate and severe renal impairment, respectively. The apparent clearance of *d*-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), while it was reduced by 48% in patients with moderate (ClCr 30 to 50 mL/min, n=9), and by 66% in patients with severe renal impairment (ClCr <30 mL/min, n=5). No studies have been conducted in patients on dialysis.

Genetic Polymorphism: A small percentage of the general population (about 7% of Caucasians, 2% of African Americans, and about 2% of Asians) is deficient in CYP2D6 enzyme activity, and is considered poor metabolizers of CYP2D6 metabolized drugs. Nebivolol undergoes hepatic metabolism mainly (up to 77% in animals and 75% in humans) by CYP2D6, and is subject to this genetic polymorphism.

Poor CYP2D6 metabolizers have been shown to have markedly higher plasma concentrations of nebivolol and less oxidative related metabolites compared with people with normal CYP2D6 activity, while maintaining their ability to glucuronidate nebivolol.

STORAGE AND STABILITY
Store at controlled room temperature (15 - 30°C). Protect from light.

SPECIAL HANDLING INSTRUCTIONS
No special handling is required.

DOSAGE FORMS, COMPOSITION AND PACKAGING
BYSTOLIC (nebivolol tablets) is available as tablets for oral administration containing nebivolol hydrochloride equivalent to 2.5, 5, 10, and 20 mg of nebivolol, and will be supplied in bottles of 30 tablets.

BYSTOLIC contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake (10 mg and 20 mg only), 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.

BYSTOLIC tablets are triangular-shaped, biconvex, unscored, differentiated by colour and are engraved with "**FL**" on one side and the number of mg (2.5, 5, 10, or 20) on the other side. The 2.5 mg tablet is light blue, the 5 mg tablet is beige, the 10 mg tablet is pinkish-purple, and the 20 mg tablet is light blue.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

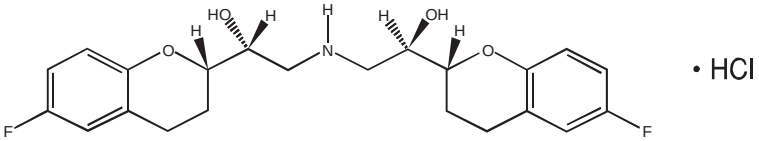
Drug Substance

Proper name: Nebivolol hydrochloride

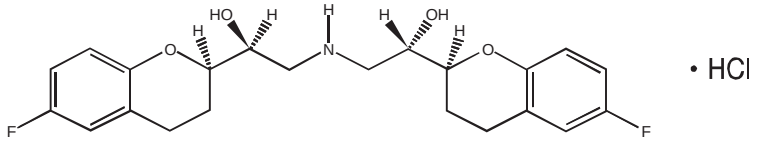
Chemical name: (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]- 2,2'-iminodiethanol hydrochloride.

Molecular formula and molecular mass: $C_{22}H_{25}F_2NO_4$•HCl with a MW: 441.90 g/mol

Structural formula: Nebivolol is a racemic mixture of *d*-Nebivolol and *l*-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol, respectively.



SRRR - or *d*-nebivolol hydrochloride



RSSS - or *l*-nebivolol hydrochloride

Physicochemical properties: 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, methylbenzene and water. The pKa of nebivolol hydrochloride is 8.4 for the amino group.

CLINICAL TRIALS

The antihypertensive efficacy of BYSTOLIC (nebivolol tablets) as monotherapy has been investigated in three randomized, double-blind, multi-centre, placebo-controlled trials at doses ranging from 1.25 to 40 mg for 12 weeks (Studies 1, 2 and 3). In two separate combination studies, additional antihypertensive effect was demonstrated when BYSTOLIC was administered concomitantly with either thiazide diuretics or ACE inhibitors. Sustained efficacy over 24 hours has been shown for BYSTOLIC once-daily dosing schedule.

Monotherapy Studies

Study demographics and trial design

Table 6: Summary of Patient Demographics for Clinical Trials in Treatment of Mild to Moderate Essential Hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (ITT/completed study)	Median age (Range)	Sex (M - Male, F - Female)
Study 1	Double-blind, placebo-controlled	Oral Placebo, BYSTOLIC 1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 30/40 mg 28 to 42-day, single-blind placebo run-in, 12 weeks double-blind treatment	Placebo 81/67 BYSTOLIC 1.25 mg 83/68, 2.5 mg 82/68, 5 mg 165/148, 10 mg 166/133, 20 mg 166/144, 30/40 mg 166/149 Total 909/777	54 years (22–84)	M: 518 (57%) F: 391(43%)
Study 2	Double-blind, placebo-controlled	Oral Placebo, BYSTOLIC 5 mg, 10 mg, 20 mg. 28 to 42-day single-blind placebo run-in, 12 weeks double-blind treatment	Placebo 75/61 BYSTOLIC 5 mg 244/218, 10 mg 244/206, 20 mg 244/217 Total 807/702	53 years (22–82)	M: 432 (53.5%) F: 375 (46.5%)
Study 3	Double-blind, placebo-controlled	Oral Placebo, BYSTOLIC 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg 14 to 42-day, single-blind, placebo run-in, 12 weeks double-blind treatment	Placebo 49/41 BYSTOLIC 2.5 mg 49/42, 5 mg 50/41, 10 mg 51/47, 20 mg 50/45, 40 mg 51/43 Total 300/259	50 years (26–79)	M: 136 (45.3%) F: 164 (54.7%)

The three monotherapy trials included a total of 2,016 patients (1,811 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 12 weeks. Two of these monotherapy trials (Studies 1 and 2) studied 1,716 patients in the general hypertensive population with a mean age of 54 years, 55% males, 26% non-Caucasians, 7% diabetics and 6% genotyped as poor metabolizers (PMs). The third monotherapy trial (Study 3) studied 300 Black hypertensive patients with a mean age of 51 years, 45% males, 14% diabetics, and 2.3% as PMs.

Study Results

The primary endpoint in the three monotherapy trials was the change from baseline in trough sitting DBP as Week 12. Change from baseline in trough sitting systolic blood pressure (SBP) was used as a secondary endpoint. Blood pressure reductions by dose for each study are presented in Table 7. The least square (LS) mean reduction in trough sitting DBP was significantly greater with BYSTOLIC doses ≥5 mg than with placebo in all studies. BYSTOLIC reduced trough sitting DBP in patients regardless of race, age or sex.

The LS mean reduction in trough sitting SBP was significantly greater with BYSTOLIC than with placebo for all doses in Study 1, the 20 mg dose in Study 2 and the 10 mg and 20 mg doses in Study 3.

Table 7: Analysis of Sitting Diastolic and Systolic Blood Pressure (mmHg) at Trough at Week 12

Study	Treatment group	Placebo	BYSTOLIC 2.5 mg	BYSTOLIC 5 mg	BYSTOLIC 10 mg	BYSTOLIC 20 mg
Study 1	**Trough Sitting Diastolic BP (mmHg)**					
	LS Mean Change[a]	-2.9	-8.5	-8.4	-9.2	-9.8
Mean Baseline SBP/DBP: 153.1/99.5 mmHg	p-value[a,b]		<0.001	<0.001	<0.001	<0.001
	Trough Sitting Systolic BP (mmHg)					
	LS Mean Change[a]	+2.2	-6.3	-5.9	-7.0	-6.5
	p-value[a,b]		<0.001	<0.001	<0.001	<0.001
Study 2	**Trough Sitting Diastolic BP (mmHg)**					
	LS Mean Change[a]	-4.6	--	-7.8	-8.5	-9.1
Mean Baseline SBP/DBP: 151.3/99.0 mmHg	p-value[a,b]		--	0.002	<0.001	<0.001
	Trough Sitting Systolic BP (mmHg)					
	LS Mean Change[a]	-0.4	--	-4.2	-3.5	-6.7
	p-value[a,b]		--	0.035[NS]	0.086[NS]	<0.001
Study 3	**Trough Sitting Diastolic BP (mmHg)**					
	LS Mean Change[a]	-2.8	-5.7	-7.7	-8.9	-8.9
Mean Baseline SBP/DBP: 152.2/100.2 mmHg	p-value[a,b]		0.084[NS]	0.004	<0.001	<0.001
	Trough Sitting Systolic BP (mmHg)					
	LS Mean Change[a]	-0.4	-1.9	-3.0	-6.4	-7.6
	p-value[a,b]		0.611[NS]	0.383[NS]	0.044	0.005

[a]From an ANCOVA with factor treatment and covariates (baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group).
[b]Based on pairwise comparison of treatment vs. placebo
LS=least-squares, NS=not significant

The blood pressure lowering effect of BYSTOLIC was seen within two weeks of treatment and was maintained over the 24-hour dosing interval with trough-to-peak ratios for diastolic response ranging from 60 - 90% in all studies for BYSTOLIC doses of 2.5 - 20 mg.

Twenty-eight days after cessation of BYSTOLIC treatment, blood pressure returned toward baseline, without however reaching that level. There was no evidence of rebound hypertension after abrupt cessation of therapy.

After 12 weeks of treatment, the response rate in Study 1 was 50.0% for BYSTOLIC 2.5 mg, 50.3% for 5 mg, 53.6% for 10 mg and 59.6% for 20 mg *vs.* 24.7% for placebo (all p≤0.001). The

response rates in Study 2 were 49.3%, 66.0%, 66.8% and 68.9% in the placebo, BYSTOLIC 5 mg, 10 mg, and 20 mg groups, respectively (all p≤0.009). In Study 3, the percentage of responders were 36.7%, 58.0%, 58.8% and 64.0% in the BYSTOLIC 2.5 mg, 5 mg, 10 mg and 20 mg groups compared with a placebo response rate of 26.5% (p≤0.002 for BYSTOLIC doses of 5 mg and above).

Heart rate was assessed in all studies. In Study 1, mean seated trough heart rate changes were +0.2, -4.3, -6.5, -6.5 and -9.7 bpm for placebo, BYSTOLIC 2.5 mg, 5 mg, 10 mg and 20 mg, respectively. The reductions observed with BYSTOLIC were significant as compared to placebo (p<0.001 for doses 2.5 to 20 mg). Heart rate was also significantly lowered for all doses in Study 2. Mean placebo-subtracted reductions ranged from -5.1 bpm to -7.2 bpm (p<0.001 *vs.* placebo). In Study 3, reductions in sitting heart rate at peak plasma drug level for BYSTOLIC 5 mg, 10 mg, and 20 mg were statistically significant (p<0.015).

Concomitant Therapy Studies

Diuretics

BYSTOLIC 1 mg, 5 mg and 10 mg and hydrochlorothiazide (HCTZ) 12.5 mg, and 25 mg were studied alone and in combination in a 12-week, randomized, double-blind, placebo-controlled, parallel-group, 12-arm factorial study including 240 patients with mild to moderate essential hypertension (mean baseline sitting SBP/DBP of 157.7/100.8 mmHg). The average age was 52 and 66% of the patients were male. The primary efficacy endpoint was the change from baseline in trough sitting DBP at Week 12. Blood pressure reductions by dose are presented in Table 8. The mean reductions in trough sitting DBP (primary efficacy endpoint) from baseline were statistically significant for all treatment arms (p<0.05 *vs.* baseline). All active treatment (monotherapy and combination) were also found to be more effective than placebo (p<0.05). No statistical analysis for comparison *vs.* placebo was performed for the secondary endpoint, trough sitting SBP.

Table 8: Summary of Mean Changes from Baseline in Trough Sitting Blood Pressure (SBP/DBP) (mmHg) for Patients Receiving BYSTOLIC, HCTZ, or BYSTOLIC/HCTZ in Combination

	HCTZ		
BYSTOLIC	**0 mg**	**12.5 mg**	**25 mg**
0 mg	-0.2 / -1.4	-11.2 / -4.6	-15.0 / -5.8
1 mg	-6.5 / -5.5	-14.1 / -9.4	-19.4 / -10.3
5 mg	-16.7 / -8.5	-16.0 / -9.9	-17.9 / -12.4
10 mg	-17.6 / -13.8	-21.9 / -12.6	-29.0 / -15.3

N=20 patients/arm; within treatment comparisons to baseline were statistically significant for all treatment groups with p-value ≤0.003.
DBP: all pairwise comparisons vs. placebo were statistically significant with p-value <0.05
SBP: comparisons vs. placebo not assessed

Significant reductions in trough sitting DBP from baseline were observed as early as week two. Significant increases in the percentage of patients who responded to treatment were obtained with BYSTOLIC in combination with HCTZ, as compared to placebo (p<0.02). The response rates were 60%, 85%, 80% and 85% for the 5 mg/12.5 mg, 5 mg/25 mg, 10 mg/12.5 mg and 10 mg/25 mg BYSTOLIC/HCTZ combinations, respectively, and 15% for placebo. BYSTOLIC 5 mg and 10 mg in combination with HCTZ, 12.5 mg and 25 mg, provided heart rate reductions of -3 bpm to -10 bpm (p<0.05 *vs.* placebo) for all combination groups excluding BYSTOLIC 5 mg/HCTZ 25 mg.

Angiotensin Converting Enzyme (ACE) Inhibitors

BYSTOLIC 5 mg to 20 mg and lisinopril 10 mg to 40 mg were studied alone and in combination in a 12-week, multi-centre, randomized, double-blind, placebo- and active-controlled, parallel-group, 4-arm study including 656 patients with stage 2 diastolic hypertension (DBP ≥ 100 mm Hg). The mean baseline sitting SBP/DBP was 163.8/104.4 mmHg. The mean age of patients was 49.3 years, 57.8% were males, 14.9% were diabetic and 38.0% were non-Caucasian. The primary efficacy endpoint was the change from baseline in trough sitting DBP at Week 6 and the secondary efficacy endpoint was the change from baseline in trough sitting SBP at Week 6.

Blood pressure reductions by treatment group are presented in Table 9. The combination of BYSTOLIC and lisinopril was significantly more effective in lowering DBP than BYSTOLIC or lisinopril alone (p≤0.001). All active treatments (combination and monotherapy) were more effective than placebo (p≤0.0013). The combination treatment group showed a statistically significant greater reduction in DBP compared with the average effect of BYSTOLIC and lisinopril (p<0.0001). Significant reductions in trough sitting DBP from baseline were observed as early as two weeks of treatment.

Table 9: Analysis of Sitting Diastolic and Systolic Blood Pressure (mmHg) at Trough at Week 6

		Placebo (N=93)	BYSTOLIC + Lisinopril (N=189)	BYSTOLIC (N=185)	Lisinopril (N=189)
Trough Sitting Diastolic BP (mmHg)					
Mean Baseline DBP: 104.4 mmHg	Mean Change	-8.0	-17.2	-13.3	-12.0
	LSMD* [a]	9.0	--	3.3	5.1
	p-value 1[a]	<0.0001	--	0.0010	<0.0001
	p-value 2[b]	--	<0.0001	--	--
Trough Sitting Systolic BP (mmHg)					
Mean Baseline SBP: 163.8 mmHg	Mean Change	-9.9	-19.2	-14.4	-16.1
	LSMD* [a]	10.0	--	3.5	3.2
	p-value 1[a]	<0.0001	--	0.0470	0.0704
	p-value 2[b]	--	0.0278	--	--

ANCOVA, analysis of covariance; LSMD, least squares mean difference

* Analysis was based on ANCOVA model with treatment group and study center as factors and baseline value as a covariate

a [*] comparing the combination group vs. placebo, the combination group vs. BYSTOLIC, and the combination group vs. lisinopril.

b [*] comparing the combination group vs. the average of BYSTOLIC and lisinopril.

The combination of BYSTOLIC and lisinopril was significantly more effective in lowering SBP than BYSTOLIC alone (p=0.0470). The combination showed a numerically greater reduction in SBP than lisinopril alone (p=0.0704). All active treatments (combination and monotherapy) were found to be more effective than placebo (p≤0.0033). The combination treatment group showed a statistically significant greater reduction in SBP compared with the average effect of BYSTOLIC and lisinopril (p=0.0278).

After 6 weeks of treatment, the response rate (BP < 140/90 mmHg or < 130/80 mmHg for diabetic patients) was significantly greater for patients treated with the combination of BYSTOLIC and lisinopril at 33.9%, compared to 21.6%, 21.7% and 7.5% for patients treated with BYSTOLIC monotherapy, lisinopril monotherapy or placebo respectively (all p≤0.0031).

Geriatrics (≥ 65 years of age)

Of the 2,016 patients in the placebo-controlled monotherapy studies, 375 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.

DETAILED PHARMACOLOGY

Nebivolol is a racemic mixture containing equal amounts of two enantiomers, *d*-nebivolol and *l*-nebivolol. It is a selective β_1-adrenergic antagonist with vasodilating properties. The *d*-enantiomer provides selective β_1-adrenergic receptor blockade, whereas *l*-nebivolol possesses vasodilating properties thought to be attributable to nitric oxide modulation via the L-arginine-nitric oxide pathway.

Preclinical pharmacology studies show that nebivolol binds to human cardiac β_1-adrenergic receptors with high affinity (K_i = 0.7 nM). Nebivolol antagonizes β_1-adrenergic receptor mediated responses in isolated tissues from guinea pigs and dogs and in rat heart cell cultures *in vitro.* Nebivolol also effectively inhibits various β_1-adrenergic receptors responses *in vivo* in rodent, cat and dog models. Nebivolol retains β_1-adrenergic receptor selectivity in a wide variety of these test systems. Nebivolol does not have relevant effects in other test systems, such as α-adrenergic and muscarinic receptor systems.

Nebivolol, dose-dependently, reduces blood pressure in spontaneously hypertensive rats following acute and repeated administration and does not produce an increase in peripheral vascular resistance or decrease in cardiac output in anesthetized dogs, but at peak after 10 mg/kg orally, a 38% decrease of cardiac output was observed as compared to baseline in awake dogs.

Mechanistic studies in isolated coronary arteries showed that nebivolol and, more potently, *l*-nebivolol induce the release of nitric oxide from vascular endothelium *in vitro*. In both pre-clinical and clinical studies, nebivolol-induced vasodilation can be blocked by inhibitors of nitric oxide synthase. This property appears to contribute to the pharmacological profile of nebivolol.

In addition, nebivolol protected myocardial cells from calcium overload and preserved cardiac function in ischemic myocardium. Nebivolol demonstrated antiarrhythmic activity *in vivo*, suppressing experimentally induced arrhythmias produced by ischemia and reperfusion (rat and dog) as well as those induced by aconitine (rat) and by ouabain (guinea pig), but it also increased atrial conduction time thus leading to increased PQ and PR intervals and significantly decreased HR. Moreover, nebivolol increased the ventricular fibrillation threshold in anesthetized open-chest guinea pigs and dogs, but it increased AV blocks and branch bundle block occurence.

Nebivolol seems to have low affinity for α-adrenoreceptors in *in vitro* receptor binding assays ($K_i \geq 295$ nM) at target therapeutic concentrations, and had apparently little activity at α_1-adrenergic receptors in *in vivo* and *ex vivo* functional assays ($IC_{50} \geq 1.4$ μM). Nebivolol was found to lack appreciable activity or to be inactive on responses mediated by serotonin, histamine, dopamine, acetylcholine (muscarinic and nicotinic), angiotensin II and bradykinin receptor activation, but bound at higher concentrations to β_2-adrenergic, serotonin (5HT1A) and dopamine receptors (D4.4) (K_i = 4.5 nM, 15.1 nM, 56.2 nM respectively). In addition, receptor binding or transactivation assays also demonstrated that nebivolol did not bind to opioid, GABAergic and various hormone receptors, such as the estrogen receptor. Therefore at

therapeutic plasma concentrations, nebivolol has little activity at other receptors that would produce vasodilation except for β_2-adrenergic, serotonin (5HT1A) and dopamine receptors (D4.4).

Nebivolol is predominantly metabolized in humans and in animals by CYP2D6 (75%) and to a lesser extent by CYP3A4 (16-20%) [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics]. *In vitro* studies have demonstrated that nebivolol has an inhibitory effect on cytochrome P450 isozymes including CYP3A4/5 (Ki: 13 μM), CYP2A6 (Ki: 49 μM), CYP2C8 (Ki: 55 μM), CYP2B6 (Ki: 92 μM), CYP1A2 (Ki: 92 μM), CYP2C9 (Ki: 110 μM), CYP2C19 (Ki: 130 μM) and CYP4A9/11 (Ki: 180 μM). In addition, nebivolol was also found to significantly increase (by 50%) the activity of CYP2E1. Given the C_{max}/K_i ratios, it is unlikely that these inhibitory effects *in vitro* would translate into clinically meaningful inhibitory effects.

TOXICOLOGY

Acute Toxicity

Single-dose study findings revealed that nebivolol has a low order of acute toxicity by the oral route. The highest non-lethal dose levels tested were approximately 80 and >260 times the maximum recommended human dose (MRHD) for the rat and dog, respectively, based on body surface area. Single-dose studies at high doses of nebivolol showed that female rats were more sensitive than male rats, while there were no sex differences with mice or dogs.

Long Term Toxicity

Repeated dose oral toxicology studies of nebivolol were conducted in mice for 3 months and in rats and dogs for 3, 6 and 12 months duration. Target organs for repeat dose studies in rodents were spleen, adrenals, gonads, lungs, and lymph nodes, with decreases in hemoglobin, hematocrit, red blood cells, cholesterol, triglycerides, and phospholipids and an increase in potassium. The no-observed-adverse-effect level (NOAEL) for these effects in the one-year rat study was 5 mg/kg/day. The AUC values for 5 mg/kg/day were 5.6- and 7.2- (extensive metabolizers) and 0.17- and 0.23- (poor metabolizers) times the maximum anticipated human exposure for a 20 mg clinical dose for male and female rats, respectively. The target organs for nebivolol in dogs were spleen and heart. The changes in ECG reported in dog studies included the prolongation of QTc and QRS intervals at ≥20 and 40 mg/kg in the 6- and 12-month studies, respectively. A lengthening of the PQ interval was evident at ≥20 and ≥10 mg/kg, respectively. These doses were at least ≥17 times the MRHD. The NOAEL for the ECG changes in the 12-month study was 2.5 mg/kg, which corresponds to ~2 times the MRHD based on body surface area.

Carcinogenesis

In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed in male mice at 40 mg/kg/day (10 times the MRHD based on body surface area), but not at 10 mg/kg/day. This finding was unique to mice (*i.e.*, not seen in rats or dogs). Relative exposures for male and female mice, respectively, at 40 mg/kg/day were 343- and 310- (extensive metabolizers) and 11- and 10- (poor metabolizers) times the maximum anticipated human exposure for a 20 mg clinical dose. At the 10 mg/kg/day dose, which did not show an increase in Leydig cell tumors, relative exposures were 37- (extensive metabolizers) and 1- (poor metabolizers) times the maximum anticipated human exposure for a 20 mg clinical dose. Development of testicular Leydig cell hyperplasia and adenomas were associated with an increase in serum LH level secondary to nebivolol-related

decrease in serum testosterone. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol up to 40 mg/kg/day; relative exposures for males and females, respectively, at 40 mg/kg/day were 271- and 150- (extensive metabolizers) and 8- and 4- (poor metabolizers) times the maximum anticipated human exposure for a 20 mg clinical dose.

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).

Reproduction and Development
Effects on spermatogenesis were seen in male rats and mice at ≥40 mg/kg/day (20 and 10 times the MRHD, respectively, based on body surface area). 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.

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 (2.5 times the MRHD based on body surface area), 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 (10 and 20 times the MRHD based on body surface area), 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 (20 times the MRHD based on body surface area). 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 (20 times the MRHD based on body surface area).

REFERENCES

1. Lacourcière Y, Lefebvre J, Poirier L, et al. Treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone and in combination: a randomized, double-blind, placebo-controlled, factorial-design trial. American Journal of Hypertension 1994;7:137–45.
2. Weiss RJ, Weber MA, Carr AA, et al. A randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of nebivolol, a novel beta-blocker, in patients with mild to moderate hypertension. Journal of Clinical Hypertension 2007;9:667–76.
3. Saunders E, Smith WB, DeSalvo KB, et al. The efficacy and tolerability of nebivolol in hypertensive African American patients. Journal of Clinical Hypertension 2007;9:866–75.
4. Greathouse M. Nebivolol efficacy and safety in patients with stage I-II hypertension. Clinical Cardiology 2010;33(4):E20-E27.
5. Weber MA, Basile J, Stapff M, et al. Blood Pressure Effects of Combined β-Blocker and Angiotensin Converting Enzyme Inhibitor Therapy Compared with the Individual Agents: A Placebo-Controlled Study with Nebivolol and Lisinopril. Journal of Clinical Hypertension 2012;14:588–592.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BYSTOLIC®
(nebivolol tablets)

Read this carefully before you start taking **Bystolic**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment. Ask whether there is any new information about **Bystolic**.

What is Bystolic used for?

Bystolic is used to treat high blood pressure (also known as hypertension) in adults. It can be used alone or with other medicines.

How does Bystolic work?

Bystolic belongs to a group of drugs called "beta blockers."

- It makes your heart beat more slowly and less forcefully.
- It lowers your blood pressure by relaxing your blood vessels so that your blood flows more easily.

This medicine does not cure your disease but helps to control it.

What are the ingredients in Bystolic?

Medicinal ingredients: nebivolol (as nebivolol hydrochloride).

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake (10 mg and 20 mg only), 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.

Bystolic comes in the following dosage forms:

Tablets: 2.5 mg (light blue), 5 mg (beige), 10 mg (pinkish-purple) and 20 mg (light blue)

Do not use Bystolic if you:

- Are allergic to nebivolol or any of the other ingredients in BYSTOLIC.
- Have heart failure and you notice that your symptoms are getting worse. For example you feel more tired, are out of breath more often, or have swelling of the ankles.
- Have severe heart damage and your heart is not able to pump enough blood to meet your body's needs.
- Have a slow or irregular heart beat.
- Have an abnormal heart rate or rhythm.
- Have a problem with your heart's electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).
- Have severe liver disease.
- Have serious problems with blood flow in your feet and legs (peripheral artery disease).

- Have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption
- You are 18 years and younger.

To make sure you take the drug properly and don't have side effects, talk to your healthcare professional before you take Bystolic. Talk about any health conditions or problems you may have, including if you:

- Have asthma or other lung problems (like bronchitis or emphysema).
- Have a history of heart problems.
- Have a history of fainting.
- Have diabetes and take medicine to control your blood sugar or have low blood sugar (hypoglycemia).
- Have a condition called pheochromocytoma (a tumour of the adrenal gland).
- Have thyroid problems.
- Have liver or kidney problems.
- Have had allergic reactions or have allergies.
- Are pregnant or trying to become pregnant. Bystolic is not usually recommended for use during pregnancy. Your doctor will consider the benefit to you versus the risk to your unborn baby.
- Are breastfeeding. You should not breastfeed while using Bystolic.
- Are scheduled for surgery and will be given an anesthetic.
- Develop a skin rash while taking Bystolic.

Other warnings you should know about:

Do not stop taking Bystolic suddenly. This could cause chest pain or a heart attack. If your doctor decides that you should stop taking Bystolic, your dose may be reduced so that you need to use less and less before you stop the medication completely.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to BYSTOLIC.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following drugs may interact with Bystolic:

- Drugs used for lowering blood pressure:
  - ACE inhibitors (such as lisinopril)
  - Calcium channel blockers (such as verapamil and diltiazem)
  - Clonidine
- Drugs used to treat depression and mood disorders (such as fluoxetine, paroxetine, and venlafaxine)
- Anesthetic drugs used during surgery (such as ether and cyclopropane)
- Drugs used to treat diabetes such as insulin and oral medicines. You could become less aware of the symptoms of low blood sugar.

- Drugs used to treat heartburn and ulcers (such as cimetidine)
- Antidiuretic drugs used to reduce the fluid build-up in your body (such as hydrochlorothiazide, furosemide and spironolactone)
- Sildenafil, a drug used to treat erectile dysfunction
- Drugs used to treat HIV/AIDS
- Drugs used to treat heart rhythm disorders (such as amiodarone, disopyramide, flecainide digoxin)
- Dexamethasone, a steroid drug used to treat inflammation
- Rifampin used to treat tuberculosis
- Fingolimod, a medicine used to treat multiple sclerosis

How to take Bystolic:

Take Bystolic:

- Exactly as prescribed
- Everyday
- Once a day, at about the same time each day
- With or without food

Usual Adult dose:

Starting daily dose: 5 mg once a day
Maximum daily dose: 20 mg once a day

Your doctor may:

- start you on a different dose or change your dose over time depending on how Bystolic works for you.
- add another medicine like a diuretic (water pill) or an ACE inhibitor for you to take along with Bystolic to treat your high blood pressure.

Do **NOT** stop taking Bystolic or change your dose without consulting your doctor. This can be dangerous.

Overdose:

If you think you have taken too much Bystolic, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose, carry on and take your next dose at the usual time. **Do NOT** double the dose.

What are the possible side effects from taking Bystolic?

These are not all the possible side effects you may feel when you are taking Bystolic. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions

Side effects may include:

- Cough
- Diarrhea
- Dizziness
- Dry mouth
- Headache
- Joint and back pain
- Nausea
- Stuffy nose and colds
- Tiredness
- Trouble sleeping

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
• **Bradycardia**: decreased heart rate that causes you to be dizzy or faint		✓	
• **Chest pain**			✓
UNCOMMON			
• **Allergic reactions**: rash, swelling of the lips, face or neck, difficulty breathing or speaking			✓
• **Heart attack**: chest pain, squeezing or pressure, fast or irregular heartbeat, nausea, trouble breathing, sweating			✓
• **Heart conduction disorders**: feeling lightheaded, dizzy, or passing out			✓
• **Hypotension (low blood pressure)**: dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up		✓	
• **Irregular heart beat or heart palpitations (skipped beats)**		✓	
• **Leg swelling from fluid retention**		✓	

• **Memory problems**		✓	
• **Shortness of breath**		✓	
• **Skin reactions:** rash	✓		
• **Vision problems**	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15º to 30ºC).

Protect from light

Keep out of reach and sight of children

If you want more information about Bystolic:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.allergan.ca, or by calling 1-800-668-6424.

This leaflet was prepared by Forest Laboratories Canada Inc.

Last Revised: June 16, 2016

Bystolic® is a registered trademark of Forest Laboratories, LLC, an Allergan affiliate, used under license by Allergan Pharma Co.