

## PRODUCT MONOGRAPH

Pr **BYSTOLIC**<sup>®</sup>

Nebivolol Tablets

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

Antihypertensive Agent

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**PrBYSTOLIC®**  
Nebivolol Tablets

(as nebivolol hydrochloride)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
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**<sup>®</sup> (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**<sup>®</sup> may need to be reduced.

### Cardiovascular

#### **Abrupt Cessation of Therapy**

Do not abruptly discontinue **BYSTOLIC**<sup>®</sup> 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  $\beta$ -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  $\beta$ -blockers, when discontinuation of **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> should be discontinued stepwise over a shorter time and under closer observation.

If the angina worsens or acute coronary insufficiency develops, re-start **BYSTOLIC**<sup>®</sup> promptly,

at least temporarily.

### **Decreased Heart Rate and PR Interval Prolongation**

Like other  $\beta_1$ -blocking agents, **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> [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**<sup>®</sup> from unopposed vagal activity remaining after blockade of  $\beta_1$ -adrenergic receptors; in such cases, dosage should be reduced.

### **Peripheral Artery Disorders**

$\beta$ -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  $\beta$ -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**<sup>®</sup> should be used with caution in patients subject to hypoglycemic episodes since  $\beta$ -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

Nonselective  $\beta$ -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. **BYSTOLIC**<sup>®</sup> is  $\beta_1$ -selective; however, it is not known whether **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> have not been adequately appraised.  $\beta$ -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  $\beta$ -blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

### **Pheochromocytoma**

**BYSTOLIC**<sup>®</sup> should be used with caution and only after pretreatment with  $\alpha$ -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**<sup>®</sup> 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  $\beta$ -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  $\beta$ -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  $\alpha$ -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  $\beta$ -adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using **BYSTOLIC**<sup>®</sup> with anesthetic agents that depress the myocardial function, such as ether, cyclopropane, and trichloroethylene [see DRUG INTERACTIONS]. Some patients receiving  $\beta$ -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  $\beta$ -blocking effects of **BYSTOLIC**<sup>®</sup> can be reversed by  $\beta$ -agonists, *e.g.*, dobutamine or isoproterenol.

If  $\beta$ -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**<sup>®</sup> has not been studied in patients receiving dialysis and is therefore not recommended for use in this patient population [see DOSAGE AND ADMINISTRATION, and

### **Respiratory**

#### **Bronchospastic Disease**

In general, patients with bronchospastic pulmonary disease should not receive  $\beta$ -blockers. However, because of its relative  $\beta_1$ -selectivity, **BYSTOLIC**<sup>®</sup> may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since  $\beta_1$ -selectivity is not absolute, the lowest possible dose of **BYSTOLIC**<sup>®</sup> should be employed, a  $\beta_2$ -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  $\beta$ -blockers, including **BYSTOLIC**<sup>®</sup>. 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  $\beta$ -adrenergic blocking agent (practolol). This syndrome has not been observed with **BYSTOLIC**<sup>®</sup>. 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**<sup>®</sup> 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  $\geq 10$  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  $\geq 5$  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 sternbrae 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  $\beta$ -blockers to produce serious adverse reactions in nursing infants, especially bradycardia, **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> (nebivolol tablets) has been evaluated for safety in more than 7,100 patients with hypertension with a clinical trial exposure to **BYSTOLIC**<sup>®</sup> in approximately 5,400 patients. Patients received **BYSTOLIC**<sup>®</sup> 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 ( $\geq 2\%$  of patients) observed with **BYSTOLIC**<sup>®</sup> were headache (7.1%), fatigue (3.6%), nasopharyngitis (3.1%), dizziness (2.9%), diarrhea (2.5%), and upper respiratory tract infections (2.1%). **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> (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**<sup>®</sup>.

### **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**<sup>®</sup> 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  $\geq 1\%$  in any BYSTOLIC<sup>®</sup> group) by Preferred Term - Placebo-Controlled, 12-Week Monotherapy Studies (Pooled Safety Population)**

System Organ Class/ Preferred Term	Placebo (n=205)	BYSTOLIC <sup>®</sup> 2.5 mg (n=131)	BYSTOLIC <sup>®</sup> 5 mg (n=459)	BYSTOLIC <sup>®</sup> 10 mg (n=461)	BYSTOLIC <sup>®</sup> 20 mg (n=460)
<b>Cardiac Disorders</b>					
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%)
<b>Eye Disorders</b>					
Vision blurred	0	2 (1.5%)	2 (0.4%)	3 (0.7%)	3 (0.7%)
<b>Gastrointestinal Disorders</b>					
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%)
<b>General Disorders and Administration Site Conditions</b>					
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%)
<b>Infections and Infestations</b>					
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%)
<b>Investigations</b>					
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%)
<b>Musculoskeletal and Connective Tissue Disorders</b>					
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%)
<b>Nervous System Disorders</b>					
Headache	12 (5.9%)	8 (6.1%)	41 (8.9%)	28 (6.1%)	28 (6.1%)

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)
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
<b>Psychiatric Disorders</b>					
Insomnia	1 (0.5%)	3 (2.3%)	3 (0.7%)	4 (0.9%)	9 (2.0%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>					
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%)
<b>Skin and Subcutaneous Tissue Disorders</b>					
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)
<b><i>Chemistry</i></b>					
AST ( $\geq 3$ X ULN)	0	0	3 (0.7%)	2 (0.4%)	4 (0.9%)
Blood urea nitrogen (BUN) ( $\geq 10.7$ mmol/L)	0	1 (0.8%)	2 (0.4%)	3 (0.7%)	2 (0.4%)
Uric acid (Male $\geq 625$ $\mu$ mol/L; Female $\geq 506$ $\mu$ mol/L)	0	0	2 (0.4%)	0	1 (0.2%)
<b><i>Hematology</i></b>					
Eosinophils ( $\geq 10\%$ )	2 (1.0%)	1 (0.8%)	8 (1.7%)	3 (0.7%)	5 (1.1%)
Hematocrit (Male $\leq 37\%$ ; Female $\leq 32\%$ )	3 (1.5%)	2 (1.5%)	4 (0.9%)	5 (1.1%)	9 (2.0%)
Hemoglobin (Male $\leq 7.1$ mmol/L; Female $\leq 5.9$ mmol/L)	1 (0.5%)	1 (0.8%)	2 (0.4%)	1 (0.2%)	4 (0.9%)
<b><i>Urinalysis</i></b>					
Protein (increase $\geq 2$ units)	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  $\mu$ mol/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**<sup>®</sup> (nebivolol tablets) is co-administered with an inhibitor, inducer, or substrate of this enzyme, the dose of **BYSTOLIC**<sup>®</sup> 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  $\beta_1$ -blocking agents, **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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,  $\alpha_2$ -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
$\alpha_2$ -adrenergic receptor agonists (e.g., clonidine, guanethidine)	T	The added $\beta$ -blocking action of <b>BYSTOLIC</b> <sup>®</sup> may produce excessive reduction of sympathetic activity.	Closely monitor patients concomitantly treated with an $\alpha_2$ -agonist. In patients who are receiving <b>BYSTOLIC</b> <sup>®</sup> and clonidine, discontinue <b>BYSTOLIC</b> <sup>®</sup> 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.	Use caution when <b>BYSTOLIC</b> <sup>®</sup> is co-administered with ACE inhibitors.

Common Name	Reference	Effect	Clinical Comments
		<p>The risk of bradycardia/sinus bradycardia was slightly increased when nebivolol was given concomitantly with lisinopril compared to administration of nebivolol alone.</p> <p>More patients showed a shift in total 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.</p>	
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 <b>BYSTOLIC</b> <sup>®</sup> is co-administered with anesthetic agents.
Antiarrhythmics (e.g., amiodarone, disopyramide, flecainide)	C, T	<b>BYSTOLIC</b> <sup>®</sup> can exacerbate the effects of myocardial depressants or inhibitors of atrioventricular conduction.	Monitor patients closely when <b>BYSTOLIC</b> <sup>®</sup> is co-administered with antiarrhythmics. Dose adjustment may be needed.
Antidiabetic agents (e.g., insulin and oral hypoglycemic agents)	C, T	$\beta$ -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.	Use caution when <b>BYSTOLIC</b> <sup>®</sup> is co-administered in patients subject to hypoglycemic episodes.
Calcium channel blockers (particularly verapamil and diltiazem, etc.)	C*, T	<p><b>BYSTOLIC</b><sup>®</sup> can exacerbate the effects of myocardial depressants or inhibitors of atrioventricular conduction.</p> <p>Cases of serious effects (e.g. bradycardia, syncope, requiring hospitalization) in patients treated with nebivolol and verapamil, diltiazem were reported.</p>	Monitor patients closely when <b>BYSTOLIC</b> <sup>®</sup> 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 <b>BYSTOLIC</b> <sup>®</sup> may need to be adjusted.
CYP2D6 inhibitors (e.g., fluoxetine, quinidine, paroxetine, propafenone and cimetidine) and substrates (e.g., thioridazine, venlafaxine)	CT, C	<p>Inhibitors or substrates of CYP2D6 increase the exposure of nebivolol.</p> <p>Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of <b>BYSTOLIC</b><sup>®</sup> to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C<sub>max</sub> for <i>d</i>-nebivolol.</p>	<p>Use caution when <b>BYSTOLIC</b><sup>®</sup> is co-administered with CYP2D6 inhibitors/substrates.</p> <p>The dose of <b>BYSTOLIC</b><sup>®</sup> may need to be reduced.</p>

Common Name	Reference	Effect	Clinical Comments
Digoxin	T, C*	Concomitant administration of <b>BYSTOLIC</b> <sup>®</sup> and digoxin can exacerbate slowing atrioventricular conduction and heart rate.  Cases of bradycardia were reported with concomitant use.	Monitor patients closely when <b>BYSTOLIC</b> <sup>®</sup> is co-administered with digoxin.
Diuretics: hydrochlorothiazide, furosemide, spironolactone	CT, C*	No pharmacokinetic interactions were observed in healthy adults between <b>BYSTOLIC</b> <sup>®</sup> (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 <b>BYSTOLIC</b> <sup>®</sup> 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 <b>BYSTOLIC</b> <sup>®</sup> (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 <i>d</i> -neбиволol.	No specific action required.
Sildenafil	CT	The co-administration of neбиволol and sildenafil decreased AUC and C <sub>max</sub> of sildenafil by 21 and 23% respectively. The effect on the C <sub>max</sub> and AUC for <i>d</i> -neбиволol was also small (<20%). Given that both agents modulate the nitric oxide pathway, vital signs were measured.	Use caution when <b>BYSTOLIC</b> <sup>®</sup> 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 neбиволol.
Valsartan	CT	Concomitant administration of <b>BYSTOLIC</b> <sup>®</sup> (20 mg once daily) and valsartan (320 mg once daily) in 30 healthy adult volunteers resulted in a 47% and 19% reduction in <i>d</i> -neбиволol C <sub>max</sub> 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 neбиволol 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**<sup>®</sup> 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**<sup>®</sup> (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**<sup>®</sup> 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 (Cl<sub>Cr</sub> less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> (nebivolol tablets) overdose. The most common signs and symptoms associated with **BYSTOLIC**<sup>®</sup> overdose are bradycardia and hypotension. Other important adverse reactions reported with **BYSTOLIC**<sup>®</sup> overdose include heart failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with  $\beta$ -blocker overdose include bronchospasm and heart block.

The largest known ingestion of **BYSTOLIC**<sup>®</sup> worldwide involved a patient who ingested up to 500 mg of **BYSTOLIC**<sup>®</sup> 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.

### 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**<sup>®</sup>.

If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other  $\beta$ -blockers, consider the following general measures, including stopping **BYSTOLIC**<sup>®</sup>, 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  $\beta_2$ -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**<sup>®</sup> (nebivolol tablets) is a cardioselective  $\beta$ -adrenergic receptor antagonist with vasodilating activity. The exact mechanism of action of its antihypertensive response has not been definitively established. The ability of  $\beta$ -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  $\alpha$ -adrenergic receptors. Nebivolol does not appear to have intrinsic sympathomimetic activity at  $\beta_1$ -adrenergic receptors.

### **Pharmacodynamics**

Nebivolol is preferentially  $\beta_1$ -selective with a 320-fold higher affinity for human cardiac  $\beta_1$ - vs.  $\beta_2$ -adrenergic receptors. In extensive metabolizers (most of the population) and at doses less than or equal to 20 mg, nebivolol is preferentially  $\beta_1$ -selective. At clinically relevant doses in extensive metabolizers, nebivolol is not expected to significantly block  $\alpha_1$ -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  $\alpha_1$ -adrenergic receptors ( $K_i$  of 330 nM). In poor metabolizers and at higher doses, nebivolol inhibits both  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. Several metabolites of nebivolol that demonstrate binding affinity at the  $\beta_1$ -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  $\beta$ -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  $\beta_1$ -blocking activity as *d*-nebivolol's  $\beta$ -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**<sup>®</sup> on electrocardiographic intervals in healthy subjects (N=67-71/group). **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> 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
C <sub>max</sub> (ng/ml)	3.5	32
T <sub>max</sub> (hr)	1.2	3.7
T <sub>1/2</sub> (hr)	12.7	56
CL/F (L/hr)	657	16

**Absorption:** **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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  $\beta$ -blocking activity of nebivolol.

**Excretion:** After a single oral administration of <sup>14</sup>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 ( $\geq 65$  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**<sup>®</sup> 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**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> 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

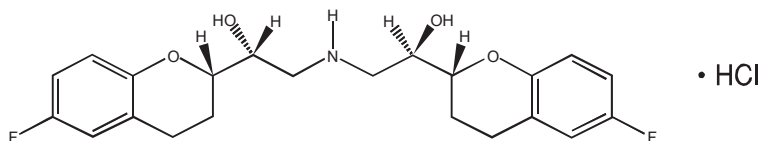
#### Drug Substance

Proper name: Nebivolol hydrochloride

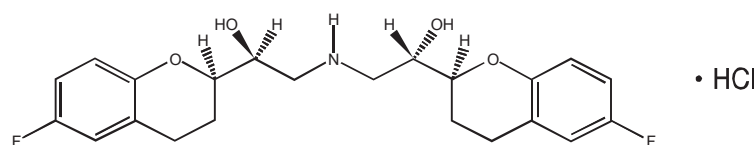
Chemical name: (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]- 2,2'-iminodiethanol hydrochloride.

Molecular formula and molecular mass: C<sub>22</sub>H<sub>25</sub>F<sub>2</sub>NO<sub>4</sub>•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]-neбиволol and [RSSS]-neбиволol, respectively.



**SRRR - or *d*-neбиволol hydrochloride**



**RSSS - or *l*-neбиволol 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 neбиволol hydrochloride is 8.4 for the amino group.

## CLINICAL TRIALS

The antihypertensive efficacy of **BYSTOLIC**<sup>®</sup> (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**<sup>®</sup> was administered concomitantly with either thiazide diuretics or ACE inhibitors. Sustained efficacy over 24 hours has been shown for **BYSTOLIC**<sup>®</sup> 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, <b>BYSTOLIC</b> <sup>®</sup> 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 <b>BYSTOLIC</b> <sup>®</sup> 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, <b>BYSTOLIC</b> <sup>®</sup> 5 mg, 10 mg, 20 mg. 28 to 42-day single-blind placebo run-in, 12 weeks double-blind treatment	Placebo 75/61 <b>BYSTOLIC</b> <sup>®</sup> 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, <b>BYSTOLIC</b> <sup>®</sup> 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 <b>BYSTOLIC</b> <sup>®</sup> 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**<sup>®</sup>, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressures (DBP) of 95 to 109 mmHg. Patients received either **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> doses  $\geq 5$  mg than with placebo in all studies. **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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 <sup>®</sup>			
			2.5 mg	5 mg	10 mg	20 mg
Study 1  Mean Baseline SBP/DBP: 153.1/99.5 mmHg	<b>Trough Sitting Diastolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	-2.9	-8.5	-8.4	-9.2	-9.8
	p-value <sup>a,b</sup>		<0.001	<0.001	<0.001	<0.001
	<b>Trough Sitting Systolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	+2.2	-6.3	-5.9	-7.0	-6.5
	p-value <sup>a,b</sup>		<0.001	<0.001	<0.001	<0.001
Study 2  Mean Baseline SBP/DBP: 151.3/99.0 mmHg	<b>Trough Sitting Diastolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	-4.6	--	-7.8	-8.5	-9.1
	p-value <sup>a,b</sup>		--	0.002	<0.001	<0.001
	<b>Trough Sitting Systolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	-0.4	--	-4.2	-3.5	-6.7
	p-value <sup>a,b</sup>		--	0.035 <sup>NS</sup>	0.086 <sup>NS</sup>	<0.001
Study 3  Mean Baseline SBP/DBP: 152.2/100.2 mmHg	<b>Trough Sitting Diastolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	-2.8	-5.7	-7.7	-8.9	-8.9
	p-value <sup>a,b</sup>		0.084 <sup>NS</sup>	0.004	<0.001	<0.001
	<b>Trough Sitting Systolic BP (mmHg)</b>					
	LS Mean Change <sup>a</sup>	-0.4	-1.9	-3.0	-6.4	-7.6
	p-value <sup>a,b</sup>		0.611 <sup>NS</sup>	0.383 <sup>NS</sup>	0.044	0.005

<sup>a</sup>From an ANCOVA with factor treatment and covariates (baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group).

<sup>b</sup>Based on pairwise comparison of treatment vs. placebo  
LS=least-squares, NS=not significant

The blood pressure lowering effect of **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> doses of 2.5 - 20 mg.

Twenty-eight days after cessation of **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 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  $p \leq 0.001$ ). The response rates in Study 2 were 49.3%, 66.0%, 66.8% and 68.9% in the placebo, **BYSTOLIC**<sup>®</sup> 5 mg, 10 mg, and 20 mg groups, respectively (all  $p \leq 0.009$ ). In Study 3, the percentage of responders were 36.7%, 58.0%, 58.8% and 64.0% in the **BYSTOLIC**<sup>®</sup> 2.5 mg, 5 mg, 10 mg and 20 mg groups compared with a placebo response rate of 26.5% ( $p \leq 0.002$  for **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 2.5 mg, 5 mg, 10 mg and 20 mg, respectively. The reductions observed with **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 5 mg, 10 mg, and 20 mg were statistically significant ( $p < 0.015$ ).

### **Concomitant Therapy Studies**

#### ***Diuretics***

**BYSTOLIC**<sup>®</sup> 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**<sup>®</sup>, HCTZ, or **BYSTOLIC**<sup>®</sup>/HCTZ in Combination**

<b>BYSTOLIC</b> <sup>®</sup>	<b>HCTZ</b>		
	<b>0 mg</b>	<b>12.5 mg</b>	<b>25 mg</b>
<b>0 mg</b>	-0.2 / -1.4	-11.2 / -4.6	-15.0 / -5.8
<b>1 mg</b>	-6.5 / -5.5	-14.1 / -9.4	-19.4 / -10.3
<b>5 mg</b>	-16.7 / -8.5	-16.0 / -9.9	-17.9 / -12.4
<b>10 mg</b>	-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  $\leq 0.003$ .

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**<sup>®</sup> 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**<sup>®</sup>/HCTZ combinations, respectively, and 15% for placebo. **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> 5 mg/HCTZ 25 mg.

### Angiotensin Converting Enzyme (ACE) Inhibitors

**BYSTOLIC**<sup>®</sup> 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  $\geq$

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**<sup>®</sup> and lisinopril was significantly more effective in lowering DBP than **BYSTOLIC**<sup>®</sup> or lisinopril alone ( $p \leq 0.001$ ). All active treatments (combination and monotherapy) were more effective than placebo ( $p \leq 0.0013$ ). The combination treatment group showed a statistically significant greater reduction in DBP compared with the average effect of **BYSTOLIC**<sup>®</sup> 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)	<b>BYSTOLIC</b> <sup>®</sup> + Lisinopril (N=189)	<b>BYSTOLIC</b> <sup>®</sup> (N=185)	Lisinopril (N=189)
<b>Trough Sitting Diastolic BP (mmHg)</b>					
<b>Mean Baseline DBP:</b> 104.4 mmHg	Mean Change	-8.0	-17.2	-13.3	-12.0
	LSMD* <sup>a</sup>	9.0	--	3.3	5.1
	p-value 1 <sup>a</sup>	<0.0001	--	0.0010	<0.0001
	p-value 2 <sup>b</sup>	--	<0.0001	--	--
<b>Trough Sitting Systolic BP (mmHg)</b>					
<b>Mean Baseline SBP:</b> 163.8 mmHg	Mean Change	-9.9	-19.2	-14.4	-16.1
	LSMD* <sup>a</sup>	10.0	--	3.5	3.2
	p-value 1 <sup>a</sup>	<0.0001	--	0.0470	0.0704
	p-value 2 <sup>b</sup>	--	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**<sup>®</sup>, and the combination group vs. lisinopril.

b [\*] comparing the combination group vs. the average of **BYSTOLIC**<sup>®</sup> and lisinopril.

The combination of **BYSTOLIC**<sup>®</sup> and lisinopril was significantly more effective in lowering SBP than **BYSTOLIC**<sup>®</sup> 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 ( $p \leq 0.0033$ ). The combination treatment group showed a statistically significant greater reduction in SBP compared with the average effect of **BYSTOLIC**<sup>®</sup> 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**<sup>®</sup> and lisinopril at 33.9%, compared to 21.6%, 21.7% and 7.5% for patients treated with **BYSTOLIC**<sup>®</sup> monotherapy, lisinopril monotherapy or placebo respectively (all  $p \leq 0.0031$ ).

### **Geriatrics ( $\geq 65$ 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*-neбиволol and *l*-neбиволol. It is a selective  $\beta_1$ -adrenergic antagonist with vasodilating properties. The *d*-enantiomer provides selective  $\beta_1$ -adrenergic receptor blockade, whereas *l*-neбиволol possesses vasodilating properties thought to be attributable to nitric oxide modulation via the L-arginine-nitric oxide pathway.

Preclinical pharmacology studies show that neбиволol binds to human cardiac  $\beta_1$ -adrenergic receptors with high affinity ( $K_i = 0.7$  nM). Neбиволol antagonizes  $\beta_1$ -adrenergic receptor mediated responses in isolated tissues from guinea pigs and dogs and in rat heart cell cultures *in vitro*. Neбиволol also effectively inhibits various  $\beta_1$ -adrenergic receptors responses *in vivo* in rodent, cat and dog models. Neбиволol retains  $\beta_1$ -adrenergic receptor selectivity in a wide variety of these test systems. Neбиволol does not have relevant effects in other test systems, such as  $\alpha$ -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 neбиволol and, more potently, *l*-neбиволol induce the release of nitric oxide from vascular endothelium *in vitro*. In both pre-clinical and clinical studies, neбиволol-induced vasodilation can be blocked by inhibitors of nitric oxide synthase. This property appears to contribute to the pharmacological profile of neбиволol.

In addition, neбиволol protected myocardial cells from calcium overload and preserved cardiac function in ischemic myocardium. Neбиволol 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, neбиволol increased the ventricular fibrillation threshold in anesthetized open-chest guinea pigs and dogs, but it increased AV blocks and branch bundle block occurrence.

Nebivolol seems to have low affinity for  $\alpha$ -adrenoreceptors in *in vitro* receptor binding assays ( $K_i \geq 295$  nM) at target therapeutic concentrations, and had apparently little activity at  $\alpha_1$ -adrenergic receptors in *in vivo* and *ex vivo* functional assays ( $IC_{50} \geq 1.4$   $\mu$ M). Neбиволol 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  $\beta_2$ -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  $\beta_2$ -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 ( $K_i$ : 13  $\mu$ M), CYP2A6 ( $K_i$ : 49  $\mu$ M), CYP2C8 ( $K_i$ : 55  $\mu$ M), CYP2B6 ( $K_i$ : 92  $\mu$ M), CYP1A2 ( $K_i$ : 92  $\mu$ M), CYP2C9 ( $K_i$ : 110  $\mu$ M), CYP2C19 ( $K_i$ : 130  $\mu$ M) and CYP4A9/11 ( $K_i$ : 180  $\mu$ M). 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  $\geq 20$  and 40 mg/kg in the 6- and 12-month studies, respectively. A lengthening of the PQ interval was evident at  $\geq 20$  and  $\geq 10$  mg/kg, respectively. These doses were at least  $\geq 17$  times the MRHD. The NOAEL for the ECG changes in the 12-month study was 2.5 mg/kg, which corresponds to  $\sim 2$  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<sup>+/−</sup>, *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  $\geq 40$  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).

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**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.

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	
<b>COMMON</b>			
• <b>Bradycardia:</b> decreased heart rate that causes you to be dizzy or faint		✓	
• <b>Chest pain</b>			✓
<b>UNCOMMON</b>			
• <b>Allergic reactions:</b> rash, swelling of the lips, face or neck, difficulty breathing or speaking			✓
• <b>Heart attack:</b> chest pain, squeezing or pressure, fast or irregular heartbeat, nausea, trouble breathing, sweating			✓
• <b>Heart conduction disorders:</b> feeling lightheaded, dizzy, or passing out			✓
• <b>Hypotension (low blood pressure):</b> dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up		✓	
• <b>Irregular heart beat or heart palpitations (skipped beats)</b>		✓	
• <b>Leg swelling from fluid retention</b>		✓	
• <b>Memory problems</b>		✓	

• <b>Shortness of breath</b>		✓	
• <b>Skin reactions: rash</b>	✓		
• <b>Vision problems</b>	✓		

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 report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*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 (15° to 30°C).

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](https://www.canada.ca/en/health-canada.html) <https://www.canada.ca/en/health-canada.html>; the manufacturer's website [www.allergan.ca](http://www.allergan.ca), or by calling 1-800-668-6424.

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