PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**PRZ-NEBIVOLOL**

Nebivolol Tablets

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

Antihypertensive Agent

Pharmaris Canada Inc.
8310-130th Street, Suite 102
Surrey, British Columbia
Canada, V3W 8J9
www.pharmaris.com

Date of Initial Authorization:
JUN 14, 2024

Submission Control No: 261499

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.	

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRZ-NEBIVOLOL (nebivolol tablets) is indicated for

- The treatment of mild to moderate essential hypertension.

PRZ-NEBIVOLOL may be used alone or concomitantly with thiazide diuretics or angiotensinconverting enzyme (ACE) inhibitors. See 9 DRUG INTERACTIONS, 4.2 Recommended Dose and Dosage Adjustment and 14 CLINICAL TRIALS.

PRZ-NEBIVOLOL is not recommended for the emergency treatment of hypertensive crises.

1.1 Pediatrics

The safety and efficacy of nebivolol in pediatric patients have not been established and therefore use in children is not recommended.

1.2 Geriatrics

No dosage adjustment is required in geriatric patients. Of the total number of patients receivingnebivolol in clinical studies, 436 (18%) were 65 years of age or older. No differences in efficacy or safety of nebivolol were observed between older and younger patients. See 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics.

2 CONTRAINDICATIONS

PRZ-NEBIVOLOL is contraindicated in patients with:

- Hypersensitivities to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Severe bradycardia (generally <50 bpm prior to start of therapy)
- Cardiogenic shock
- Decompensated cardiac failure
- Second or third degree atrioventricular (AV) block
- Sick sinus syndrome or sinoatrial block
- Severe hepatic impairment (Child-Pugh Score >B)
- Severe peripheral arterial circulatory disorders
- The rare hereditary conditions of Galactose intolerance, Lapp lactase deficiencyor glucose galactose malabsorption

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

In the treatment of mild to moderate essential hypertension, the dose of PRZ-NEBIVOLOL should be individualized to the needs of the patient

4.2 Recommended Dose and Dosage Adjustment

- For most patients, the recommended starting dose is 5 mg once daily, with or without food. Forpatients requiring further reduction in blood pressure, the dose can be increased at two-week intervals up to 20 mg once daily.

- ***Concomitant use of ACE inhibitors:*** When PRZ-NEBIVOLOL is to be co-administered with an ACE inhibitor, the lowest dose of theadded agent should be employed initially and if needed, can be then increased at two-weekintervals up to the maximum recommended dose See 9.4 Drug-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. Nebivolol has not been studied in patients receiving dialysis and is therefore not recommended for use in this patient population. See 7 WARNINGS AND PRECAUTIONS, Renal and 10.3 Pharmacokinetics .

- ***Hepatic Impairment:*** In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg oncedaily; titrate up slowly if needed. Nebivolol has not been studied in patients with severehepatic impairment and therefore is contraindicated in that population. See 2 CONTRAINDICATIONS, and 10.3 Pharmacokinetics.

- ***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 clinicaleffect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers. See 10.3 Pharmacokinetics.

4.4 Administration

Once-daily dosing has shown to sustain efficacy over 24 hours. A more frequent dosing regimen is unlikely to be beneficial. Nebivolol tablets can be taken with or without food.

4.5 Missed Dose

If patients miss a dose, they should wait until their next scheduled dose. Patients should notdouble their dose. **PRZ-NEBIVOLOL** should be taken once approximately every 24 hours.

5 OVERDOSAGE

Symptoms:
In clinical trials and worldwide post-marketing experience there were reports of nebivolol overdose. The most common signs and symptoms associated with nebivolol overdosage are bradycardia and hypotension. Other important adverse reactions reported with nebivolol overdose include heart failure, dizziness, hypoglycemia, fatigue andvomiting. Other adverse reactions associated with β-blocker overdose include bronchospasm andheart block.

The largest known ingestion of nebivolol worldwide involved a patient who ingested up to 500 mg of nebivolol 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 andvomiting. 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 effecton the pharmacokinetics of nebivolol.

If overdose occurs, provide general supportive and specific symptomatic treatment. Based onexpected pharmacologic actions and recommendations for other β-blockers, consider the following general measures, including stopping PRZ-NEBIVOLOL, 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 somecircumstances, 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-agonistand/or aminophylline.
- ***Hypoglycemia:*** Administer IV glucose. Repeated doses of IV glucose or possibly glucagon maybe required.

Supportive measures should continue until clinical stability is achieved.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients

Oral	Tablet 2.5 mg, 5 mg, 10 mg and 20 mg	Colloidal anhydrous silica, croscarmellose sodium, D&C Red #27 Lake (10 and 20 mg only), FD&C Blue #2 AL Lake, FD&C Yellow #6 Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and polysorbate 80.

PRZ-NEBIVOLOL (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 and 100 tablets.

Description

PRZ-NEBIVOLOL tablets:
2.5 mg: Light blue colored, triangular shaped, biconvex, unscored tablet engraved with “NBL” on one side and "$2^{1/2}$" on other side.
5.0 mg: Beige colored, triangular shaped, biconvex, unscored tablet engraved with “NBL” on one side and “5” on other side
10 mg: Pinkish purple colored, triangular shaped, biconvex, unscored tablet engraved with NBL on one side and “10” on other side.
20 mg: Light blue colored, triangular shaped, biconvex, unscored tablet, engraved with “NBL” on one side and “20” on other side.

7 WARNINGS AND PRECAUTIONS

General

Use with CYP2D6 Inhibitor
Nebivolol exposure increases significantly with inhibition of CYP2D6 [see 9.4 Drug-Drug Interactions]. The dose of PRZ-NEBIVOLOL may need to be reduced.

Cardiovascular
Abrupt Cessation of Therapy
Do not abruptly discontinue PRZ-NEBIVOLOL 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 diseaseagainst interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of PRZ-NEBIVOLOL 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, PRZ-NEBIVOLOL should be discontinued stepwise over a shorter time and under closer observation.

If the angina worsens or acute coronary insufficiency develops, re-start PRZ-NEBIVOLOL promptly, at least temporarily.

Decreased Heart Rate and PR Interval Prolongation
Like other β_1-blocking agents, nebivolol causes a decrease in heart rate and PR interval prolongation [see Electrocardiography]. Bradycardia and atrioventricular block have been reported with the use of nebivolol [see 8.2 Clinical Trial 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 PRinterval prolongation should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk [see 9.2 Drug Interactions Overview].

Sinus Bradycardia
Severe sinus bradycardia may occur with the use of nebivolol 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 9.4 Drug-Drug Interactions].

Driving and Operating Machinery
No studies on the effects of nebivolol on the ability to drive and use machines have been performed. Some adverse effects of a reduction in blood pressure, such as light-headedness, 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. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism
Diabetes and Hypoglycemia
PRZ-NEBIVOLOL 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 ofserum glucose levels. Nebivolol is β_1-selective; however, it is not known whether nebivolol 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 nebivolol 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 shouldbe 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

PRZ-NEBIVOLOL should be used with caution and only after pre-treatment with α-receptor blockersin patients with known or suspected pheochromocytoma.

Hepatic/Biliary/Pancreatic

Impaired Hepatic Function

Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. Nebivolol has not been studied in patients with severe hepatic impairment See 2 CONTRAINDICATIONS, 4.2 Recommended Dose and Dosage Adjustment, and 10.3 Pharmacokinetics.

Immune

Risk of Anaphylactic Reactions

While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety ofallergens 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 allergicreactions. 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 PRZ-NEBIVOLOL with anesthetic agents that depress the myocardial function, such as ether, cyclopropane, and trichloroethylene [see 9.4 Drug-Drug Interactions]. Some patients receiving β-adrenoceptor blocking drugs have been subject toprotracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has been reported.

In emergency surgery, the β-blocking effects of nebivolol 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. Nebivolol has not been studied in patients receiving dialysis and is therefore not recommended for use

in this patient population [see 4.2 Recommended Dose and Dosage Adjustment, and 10.3 Pharmacokinetics].

Respiratory

Bronchospastic Disease

In general, patients with bronchospastic pulmonary disease should not receive β-blockers. However, because of its relative β_1-selectivity, nebivolol 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 PRZ-NEBIVOLOL 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 nebivolol. 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 observedwith nebivolol. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

7.1 Special Populations

7.1.1 Pregnant Women

No studies of nebivolol were conducted in pregnant women. Use PRZ-NEBIVOLOL during pregnancy only if the potential benefit to the mother justifies the potentialrisk 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). Reproductive toxicity 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 bodysurface area basis).

7.1.2 Breast-feeding

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, PRZ-NEBIVOLOL is not recommended in nursing women. A decision should be made to discontinuenursing or discontinue the drug, taking into account the importance of the drug to the nursing mother.

7.1.3 Pediatrics (< 18 years of age)

Safety and efficacy in pediatric patients have not beenestablished and therefore use in children is not recommended.

7.1.4 Geriatrics (<65 years of age)

Of the total number of patients receiving nebivolol in clinical studies, 436 (18%) were 65 years of age or older. No differences in efficacy or safety of nebivolol were observed between older and younger patients

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Nebivolol tablets has been evaluated for safety in more than 7,100 patients withhypertension with a clinical trial exposure to nebivolol in approximately 5,400 patients. Patients received nebivolol for up to 36 months, with over 1,000 patients treated for at least6 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 nebivolol were headache (7.1%), fatigue (3.6%), nasopharyngitis (3.1%), dizziness (2.9%), diarrhea (2.5%), and upper respiratory tract infections (2.1%). Nebivolol 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 nebivolol (47/1811), and in 2.0% of patients givenplacebo (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 nebivolol.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reactionrates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

Table 2: Number (%) of Patients with Adverse Events (Incidence ≥1% in any nebivolol group) by Preferred Term - Placebo-Controlled, 12-Week Monotherapy Studies (Pooled Safety Population)

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

	Nebivolol 2.5 mg (n=131)	Nebivolol 5 mg (n=459)	Nebivolol 10 mg (n=461)	Nebivolol 20 mg (n=460)	Placebo (n=205)
Dizziness	4 (3.1%)	7 (1.5%)	12 (2.6%)	19 (4.1%)	4 (2.0%)
Carpal Tunnel Syndrome	2 (1.5%)	0	0	0	0
Psychiatric Disorders					
Insomnia	3 (2.3%)	3 (0.7%)	4 (0.9%)	9 (2.0%)	1 (0.5%)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	3 (2.3%)	5 (1.1%)	7 (1.5%)	3 (0.7%)	2 (1.0%)
Sinus Congestion	3 (2.3%)	4 (0.9%)	4 (0.9%)	1 (0.2%)	0
Dyspnea	0	1 (0.2%)	5 (1.1%)	7 (1.5%)	1 (0.5%)
Pharyngolaryngeal Pain	1 (0.8%)	1 (0.2%)	3 (0.7%)	5 (1.1%)	0
Skin and Subcutaneous Tissue Disorders					
Rash	3 (2.3%)	0	5 (1.1%)	4 (0.9%)	0

8.3 Less Common Clinical Trial Adverse Reactions

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; oralmucosal 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; lowerrespiratory tract infection

Investigations: alanine aminotransferase increased; aspartate aminotransferase increased; bloodalkaline 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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In placebo-controlled monotherapy studies, patients were reported to have laboratory abnormalities of clinical significance for the clinical laboratory parameters shown in Table 3.

Table 3: Number of Patients with Abnormal Laboratory Results of Clinical SignificanceOccurring 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 mcgmol/L; Female ≥506 mcgmol/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 □mol/L; hematocrit: 35-46%;hemoglobin: 7.4-9.7 mmol/L.

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

Triglycerides: Shifts from normal to values above the upper limit of normal (2.2 mmol/L) werereported 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, 10mg and 20 mg, respectively, as compared to 1.3% with placebo.

8.5 Post-Market Adverse 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 arresthave been reported shortly after initiation of nebivolol therapy; causality has not been established.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Nebivolol is a substrate for CYP2D6. Inhibitors, inducers or substrates of CYP2D6 alter the exposure of nebivolol. When PRZ-NEBIVOLOL is co-administered with an inhibitor, inducer, or substrate of this enzyme, the dose of PRZ-NEBIVOLOL 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 Animal Data).

Like other β_1-blocking agents, nebivolol causes a decrease in heart rate and PR interval prolongation [see Cardiovascular and Electrocardiography]. The concomitant use of PRZ-NEBIVOLOL 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, β_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.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comments
α_2-adrenergic receptor agonists (*e.g.*, clonidine, guanethidine)	T	The added β-blocking action of nebivolol may produce excessivereduction of sympathetic activity.	Closely monitor patients concomitantly treated with an α_2-agonist. In patients who are receiving PRZ-NEBIVOLOL and clonidine, discontinue PRZ-NEBIVOLOL for several

Common name	Source of Evidence	Effect	Clinical comments
			days before the gradual tapering ofclonidine.
Angiotensin converting enzyme(ACE) inhibitors	CT	No pharmacokinetic interaction was seen when nebivolol was co-administered withramipril. The risk of bradycardia/sinus bradycardiawas slightly increased when nebivolol was given concomitantly with lisinopril compared to administration of nebivolol alone. More patients showed a shift in total cholesterol and low density lipoprotein cholesterol (LDL-C) from normal to highrange when treated concomitantly with nebivolol and lisinopril compared to patients treated with each of these drugs alone.	Use caution when PRZ-NEBIVOLOL is co-administered with ACEinhibitors.
Anesthetic agents (*e.g.*, ether, cyclopropane and trichloroethylene)	T	Concomitant use with anesthetic agentswhich depress myocardial function can exacerbate myocardial depression.	Monitor patients ECG and bloodpressure closely when PRZ-NEBIVOLOL is co-administeredwith anesthetic agents.
Antiarrhythmics (*e.g.*, amiodarone, disopyramide, flecainide)	C, T	Nebivolol can exacerbate the effects of myocardial depressants or inhibitors ofatrioventricular conduction.	Monitor patients closely when PRZ-NEBIVOLOL is co-administered with antiarrhythmics. Doseadjustment may be needed.
Antidiabetic agents(*e.g.*, insulin and oral hypoglycemic agents)	C, T	β-blockers may mask some of themanifestations of hypoglycemia, particularly tachycardia.	Use caution when PRZ-NEBIVOLOL is co-administered in patients subject to hypoglycemic episodes.
Calcium channel blockers (particularly verapamil and diltiazem, etc.)	C*, T	Nebivolol can exacerbate the effects of myocardial depressants or inhibitors ofatrioventricular conduction. Cases of serious effects (e.g., bradycardia,syncope, requiring	Monitor patients closely when PRZ-NEBIVOLOL is co-administered with non-dihydropyridine calcium channel blockers.

Common name	Source of Evidence	Effect	Clinical comments
		hospitalization) in patients treated with nebivolol and verapamil, diltiazem were reported.	
CYP2D6 inducers (*e.g.*, dexamethasone, rifampin)	T	Inducers of CYP2D6 may decrease theexposure of nebivolol.	The dose of PRZ-NEBIVOLOL 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 CYP2D6increase the exposure of nebivolol. Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 daysprior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for *d*-nebivolol.	Use caution when PRZ-NEBIVOLOL is co-administered with CYP2D6 inhibitors/substrates. The dose of PRZ-NEBIVOLOL mayneed to be reduced.
Digoxin	T, C*	Concomitant administration of nebivolol and digoxin can exacerbateslowing atrioventricular conduction and heart rate. Cases of bradycardia were reported withconcomitant use.	Monitor patients closely when PRZ-NEBIVOLOL is co-administeredwith digoxin.
Diuretics: hydrochlorothiazide,furosemide, spironolactone	CT, C*	No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days)and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone (25 mg once daily for 10 days). Cases of bradycardia, hypotension and loss of consciousness were reported withconcomitant use.	Use caution when PRZ-NEBIVOLOL 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,

Common name	Source of Evidence	Effect	Clinical comments
			appropriate monitoringat treatment administration e.g., atleast overnight monitoring, is recommended.
Histamine -2 Receptor Antagonis ts	CT	The pharmacokinetics of nebivolol (5 mg single dose) were not affected by the co-administration of ranitidine (150 mg twice daily). Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of *d*-nebivolol.	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 PRZ-NEBIVOLOL® is co-administered with sildenafil. When co-administered, the effectson pulse and blood pressure were approximately the sum of the effects of sildenafil and nebivolol.
Valsartan	CT	Concomitant administration of nebivolol (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.	
Legend: C=Case Study, CT=Clinical Trial, T=Theoretical, C* = Case Report from PSUR data			

No pharmacokinetic interaction has been observed when nebivolol is concomitantly administeredwith 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).

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory testing have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Nebivolol is a cardio selective 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 bloodpressure 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 tohave intrinsic sympathomimetic activity at β_1-adrenergic receptors.

10.2 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 thanor 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. Severalmetabolites of nebivolol that demonstrate binding affinity at the β_1-adrenergic receptor have beenidentified 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.

Electrocardiography: A randomized, open-label, placebo- and active-controlled (atenolol and moxifloxacin), parallel group study was performed to assess the effect of nebivolol on electrocardiographic intervals in healthy subjects (N=67-71/group). Nebivolol 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. Nebivolol reduced heart rate and increased the PR interval as presented in Table 5.

Table 5: Maximum Placebo-Adjusted Mean Changes from Baseline During Treatment with nebivolol 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.

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

10.3 Pharmacokinetics

Table 6: Summary of *d,l*-Nebivolol Pharmacokinetic Parameters after Repeated Oral Administration of 10 mg Dose for 14 Days

	C_{max} (ng/ml)	T_{max} (hr)	$t_{½}$ (h)	AUC (ng.hr/ml)	CL/F (L/hr)
Extensive Metabolizers (EM)	3.5	1.2	12.7	19.7	657
Poor Metabolizers (PM)	32	3.7	56	663	16

Absorption

PRZ-NEBIVOLOL is an immediate release tablet. The absolute bioavailability has not been determined. Pharmacokinetic steady state is reached in 3 and 5 days in CYP2D6 extensiveand poor metabolizers, respectively.

Food does not significantly alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. PRZ-NEBIVOLOL may be administered with or withoutfood.

Distribution

In human plasma, approximately 98% of nebivolol is bound to protein (mostly toalbumin), 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 isalso 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.

Elimination

After a single oral administration of ^{14}C-nebivolol, 37% of the dose was recoveredin 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.

Animal Data

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 varietyof 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/kgorally, 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 increasedatrial 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 occurrence.

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, receptorbinding 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).

In vitro studies have demonstrated that nebivolol has an inhibitory effect oncytochrome 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.

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 wereseen in the pharmacokinetics of nebivolol in elderly (≥ 65 years) patients as compared to younger patients.

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

- ***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.

- ***Ethnic Origin*****:** Based on the results of a population pharmacokinetic analysis, no differences were observed in the pharmacokinetics of nebivolol and its glucuronide metabolites among differentraces.

- ***Hepatic Insufficiency:*** *d*-Nebivolol peak plasma concentration and exposure (AUC) increased3.5-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-foldin patients with moderate and severe renal impairment, respectively. The apparent clearance of *d*-nebivolol was unchanged following a single 5 mg dose of nebivolol in patients with mildrenal 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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

No special handling is required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Nebivolol hydrochloride

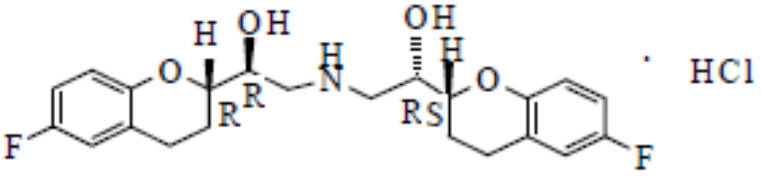
Chemical name: α,α'-[Iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] hydrochloride salt

or

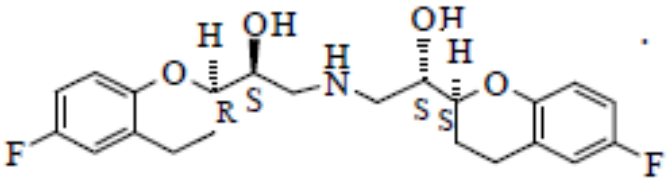
(1RS,1'RS)-1,1'-[(2RS,2'SR)-Bis(6-fluorochroman-2-yl)]-2,2'-iminodiethanol hydrochloride.

Molecular formula and molecular mass: $C_{22}H_{26}O_4NClF_2$, 441.90 g / mol

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



d-isomer (RRRS=SRRR)



l -isomer (RSSS =SSSR)

Physicochemical properties: Nebivolol hydrochloride is a white to off white powder that is very slightly soluble in water, sparingly soluble in methanol, very slightly soluble in heptane. Non-hygroscopic in nature and the pKa (base) of nebivolol hydrochloride is 8.22.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hypertension - Monotherapy

Table 7 - Summary of patient demographics for clinical trials in Treatment of Mild to Moderate Essential Hypertension

Study #	Study design	Dosage, route of administration and duration	Study subjects ITT/completed	Median age (Range)	Sex
Study 1	Double-blind, placebo-controlled	Oral Placebo, Nebivolol 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 Nebivolol 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, Nebivolol 5 mg, 10 mg, 20 mg. 28 to 42-day single-blind placebo run-in, 12 weeks double-blind treatment	Placebo 75/61 Nebivolol 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, Nebivolol 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 Nebivolol 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 antihypertensive efficacy of nebivolol (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 nebivolol

was administered concomitantly with either thiazide diuretics or ACE inhibitors. Sustained efficacyover 24 hours has been shown for nebivolol once-daily dosing schedule.

The three monotherapy trials included a total of 2,016 patients (1,811 nebivolol, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressures (DBP) of 95 to 109 mmHg. Patients received either nebivolol 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 8. The least square (LS) mean reduction in trough sitting DBP was significantly greater with nebivolol doses ≥5 mg than with placebo in all studies. Nebivolol reduced trough sitting DBP in patients regardless of race, age or sex.

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

Table 8: Analysis of Sitting Diastolic and Systolic Blood Pressure (mmHg) at Trough at Week 12

Study	Treatment group	Placebo	Nebivolol 2.5 mg	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg
Study 1	**Trough Sitting Diastolic BP (mmHg)**					
Mean Baseline SBP/DBP: 153.1/99.5 mmHg	LS Mean Change[a]	-2.9	-8.5	-8.4	-9.2	-9.8
	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)**					
Mean Baseline SBP/DBP: 151.3/99.0 mmHg	LS Mean Change[a]	-4.6	--	-7.8	-8.5	-9.1
	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)**					
Mean Baseline	LS Mean Change[a]	-2.8	-5.7	-7.7	-8.9	-8.9
	p-value[a,b]		0.084 [NS]	0.004	<0.001	<0.001

Study	Treatment group	Placebo	Nebivolol			
			2.5 mg	5 mg	10 mg	20 mg
SBP/DBP: 152.2/100.2 mmHg	**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 nebivolol was seen within two weeks of treatment andwas maintained over the 24-hour dosing interval with trough-to-peak ratios for diastolic response ranging from 60 - 90% in all studies for nebivolol doses of 2.5 - 20 mg.

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

After 12 weeks of treatment, the response rate in Study 1 was 50.0% for nebivolol 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, nebivolol 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 nebivolol 2.5 mg, 5 mg, 10 mg and20 mg groups compared with a placebo response rate of 26.5% (p≤0.002 for nebivolol 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, nebivolol 2.5 mg, 5 mg, 10 mg and 20 mg, respectively. The reductions observed with nebivolol were significant as compared to placebo (p<0.001 for doses 2.5 to 20 mg). Heart rate was also significantly lowered for all dosesin 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 nebivolol 5 mg, 10 mg, and 20 mg were statistically significant (p < 0.015).

Hypertension - Concomitant Therapy Studies

Diuretics

Nebivolol 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 9. 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).

Nostatistical analysis for comparison *vs.* placebo was performed for the secondary endpoint, troughsitting SBP.

Table 9: Summary of Mean Changes from Baseline in Trough Sitting Blood Pressure (SBP/DBP) (mmHg) for Patients Receiving nebivolol, HCTZ, or nebivolol/HCTZ in Combination

	HCTZ		
nebivolol	**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 nebivolol 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 nebivolol/HCTZ combinations, respectively, and 15% for placebo. Nebivolol 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 nebivolol 5mg/HCTZ 25 mg.

Angiotensin Converting Enzyme (ACE) Inhibitors

Nebivolol 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 10. The combination of nebivolol and lisinopril was significantly more effective in lowering DBP than nebivolol 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 groupshowed a statistically significant greater reduction in DBP compared with the average effect of nebivolol and lisinopril ($p < 0.0001$). Significant reductions in trough sitting DBP from baseline were observed as early as two weeks of treatment.

Table 10: Analysis of Sitting Diastolic and Systolic Blood Pressure (mmHg) at Trough at Week 6

		Placebo (N=93)	Nebivolol + Lisinopril (N=189)	Nebivolol (N=185)	Lisinopril (N=189)
Trough Sitting Diastolic BP (mmHg)					
Mean BaselineDBP: 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 BaselineSBP: 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 acovariate

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

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

The combination of nebivolol and lisinopril was significantly more effective in loweringSBP than nebivolol 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 theaverage effect of nebivolol and lisinopril (p=0.0278).

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

14.2 Comparative Bioavailability Studies

A double blind, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of PRZ-NEBIVOLOL 10 mg tablets (Pharmaris Canada Inc.) and [Pr]BYSTOLIC® 10 mg tablets (Allergan Inc.) was conducted in healthy adult male subjects under fasting conditions. A summary of the bioavailability data from the 22 subjects who were included in the statistical analysis is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Nebivolol (1 × 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng/mL)*(hr)	24.62 43.59 (224.32)	22.55 41.10 (229.00)	109.2	(103.2% - 115.5%)
AUC_I (ng/mL)*(hr)	27.05 69.09 (304.51)	24.20 56.49 (286.59)	111.8	(105.5% - 118.4%)
C_{max} (ng/mL)	3.80 4.26(61.59)	3.45 3.98 (80.17)	110.0	(100.7% - 120.2%)
T_{max}[3] (hr)	1.00 (0.75- 5.00)	1.00 (0.50- 3.00)		
$T_{½}$[4] (hr)	14.68 (106.06)	14.02 (80.11)		

[1] PRZ-NEBIVOLOL 10 mg (nebivolol as nebivolol hydrochloride) tablets (Pharmaris Canada Inc.)

[2] [Pr]Bystolic® 10 mg (nebivolol as nebivolol hydrochloride) tablets (Allergan Inc.), purchased in Canada

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV%) only

A double blind, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of PRZ-NEBIVOLOL 20 mg tablets (Pharmaris Canada Inc.) and [Pr]BYSTOLIC® 20 mg tablets (Allergan Inc.) was conducted in healthy adult male subjects under fasting conditions. A summary of the bioavailability data from the 21 subjects who were included in the statistical analysis is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Nebivolol (1 × 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng/mL)*(hr)	51.93 109.05(187.69)	50.82 101.99(178.57)	101.8	(96.7% - 107.2%)
AUC_I (ng/mL)*(hr)	56.69 165.58 (229.28)	54.51 134.04 (207.77)	103.8	(97.7% - 110.2%)
C_{max} (ng/mL)	7.30 8.48 (67.28)	6.335 7.25 (62.36)	118.4	(103.8% - 135.1%)
T_{max}[3] (hr)	1.25 (0.75- 6.00)	1.25 (0.50- 6.00)		
$T_{½}$[4] (hr)	15.05 18.01 (85.95)	13.89 15.58 (60.00)		

[1] PRZ-NEBIVOLOL 20 mg (nebivolol as nebivolol hydrochloride) tablets (Pharmaris Canada Inc.)
[2] [Pr]Bystolic® 20 mg (nebivolol as nebivolol hydrochloride) tablets (Allergan Inc.), purchased in Canada
[3] Expressed as either the arithmetic mean (CV%) only or the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 bodysurface 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.

***Carcinogenicity*:**
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 andadenomas 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.

Genotoxicity: Nebivolol was not genotoxic when tested in a battery of assays (Ames, *in vitro*

mouse lymphomaTK$^{+/-}$, *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 Toxicology:
Effects on spermatogenesis were seen in male rats and mice at ≥40 mg/kg/day (20 and 10 timesthe 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 timesthe MRHD based on body surface area), prolonged gestation, dystocia and reduced maternal carewere 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 toevaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal bodyweights 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 effectson 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).

17 SUPPORTING PRODUCT MONOGRAPHS

1. BYSTOLIC (tablets, 2.5 mg, 5 mg, 10 mg and 20 mg), Submission Control No. 268338, Product Monograph, AbbVie Corporation. NOV 7, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PRZ-NEBIVOLOL
nebivolol tablets

Read this carefully before you start taking **PRZ-NEBIVOLOL** and each time you get a refill.This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask there is any new information about **PRZ-NEBIVOLOL**.

What is PRZ-NEBIVOLOL used for?

- PRZ-NEBIVOLOL is used to treat high blood pressure (also known as hypertension) in adults.
- It can beused alone or with other medicines.

How does PRZ-NEBIVOLOL work?

PRZ-NEBIVOLOL belongs to a group of medicines called “beta blockers.”

- It makes your heartbeat more slowly and less forcefully.
- It lowers your blood pressure by relaxing your blood vessels so that your blood flowsmore easily.

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

What are the ingredients in PRZ-NEBIVOLOL?

Medicinal ingredients: Nebivolol (as nebivolol hydrochloride).

Non-medicinal ingredients: Colloidal anhydrous silica, croscarmellose sodium, D&C Red #27 Lake (10 mg and 20 mg only), FD&C Blue #2 AL Lake, FD&C Yellow #6 Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and polysorbate 80.

PRZ-NEBIVOLOL 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 PRZ-NEBIVOLOL if:

- You are allergic to nebivolol or any of the other ingredients in PRZ-NEBIVOLOL.
- You have heart failure and you notice that your symptoms are getting worse. For example, you feelmore tired, are out of breath more often, or have swelling of the ankles.
- You have severe heart damage and your heart is not able to pump enough blood to meet yourbody’s needs.
- You have a slow or irregular heartbeat.
- You have an abnormal heart rate or rhythm.
- You have a problem with your heart’s electrical conduction (that causes you to have

chest pain,difficulty breathing, nausea, fatigue, and fainting).
- You have severe liver disease.
- You have serious problems with blood flow in your feet and legs (peripheral artery disease).
- You have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption
- You are 18 years and younger.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRZ-NEBIVOLOL. Talk about any health conditions orproblems 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.
- Are breastfeeding or planning to breastfeed.
- Are scheduled for surgery and will be given an anesthetic.

Other warnings you should know about:

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

Driving and using machines: PRZ-NEBIVOLOL may cause light-headedness, dizziness or fainting. Before doing tasks that require special attention, wait until youknow how you respond to PRZ-NEBIVOLOL.

Pregnancy: PRZ-NEBIVOLOL is not usually recommended for use during pregnancy. It may harm an unborn baby. Your healthcare professional will decide if the benefits of taking PRZ-NEBIVOLOL outweigh the potential risks to your baby. If you discover that you are pregnant while taking PRZ-NEBIVOLOL, tell your healthcare professional **right away**.

Breastfeeding: It is not known if PRZ-NEBIVOLOL can pass into breast milk and harm a breastfed baby. You and your healthcare professional should decide if you will take PRZ-NEBIVOLOL or breastfeed. You should not do both.

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

The following may interact with PRZ-NEBIVOLOL:

- Medicines used for lowering blood pressure:
  - Angiotensin-Converting Enzyme (ACE) inhibitors (such as lisinopril)
  - Calcium channel blockers (such as verapamil and diltiazem)
  - Clonidine
- Medicines used to treat depression and mood disorders (such as fluoxetine, paroxetine, andvenlafaxine)
- Anesthetic medicines used during surgery (such as ether and cyclopropane)
- Medicines used to treat diabetes such as insulin and oral medicines. You could become less awareof the symptoms of low blood sugar.
- Medicines used to treat heartburn and ulcers (such as cimetidine)
- Antidiuretic medicines used to reduce the fluid build-up in your body (such ashydrochlorothiazide, furosemide and spironolactone)
- Sildenafil, used to treat erectile dysfunction or high blood pressure in the lungs
- Medicines used to treat HIV/AIDS
- Medicines used to treat heart rhythm disorders (such as amiodarone, disopyramide, flecainide, propafenone, digoxin)
- Dexamethasone, used to treat inflammation
- Rifampin used to treat tuberculosis
- Fingolimod, used to treat multiple sclerosis

How to take PRZ-NEBIVOLOL:

Take PRZ-NEBIVOLOL:

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

Usual dose:

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

Your healthcare professional may:

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

Do NOT stop taking PRZ-NEBIVOLOL or change your dose without consulting your healthcare professional. This canbe dangerous.

Overdose:

If you think you, or a person you are caring for, have taken too much PRZ-NEBIVOLOL, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if thereare 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 possible side effects from using PRZ-NEBIVOLOL?

These are not all the possible side effects you may have when you are taking PRZ-NEBIVOLOL. If youexperience any side effects not listed here, tell 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	
COMMON			
Bradycardia (abnormally slow heartbeat): feeling dizzy or fainting		✓	
Chest pain			✓
UNCOMMON			
Allergic reactions: rash, swelling of the lips, face or neck, difficulty breathing or speaking			✓
Myocardial infarction (heart attack): chest pain, squeezing or pressure, fast or irregular heartbeat, nausea, trouble breathing, sweating			✓

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**	
Heart conduction disorders (problems with the electrical system that controls the heart's rate and rhythm): 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 heartbeat or heart palpitations (skipped beats)		✓	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff.		✓	
Memory problems: memory loss, absentmindedness		✓	
Dyspnea (shortness of breath)		✓	
Skin reactions: rash	✓		
Vision problems: double vision, blurred vision, loss of vision, dry eyes	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enoughto interfere with your daily activities, tell 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 (15º to 30ºC).
- Protect from light
- Keep out of reach and sight of children

If you want more information about PRZ-NEBIVOLOL:

- 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/services/drugs-health-products/drug-products/drug-product-database.html) the manufacturer's website www.pharmaris.com, or by calling 1-866-913-7955.

This leaflet was prepared by Pharmaris Canada Inc.

Last Revised: JUN 14, 2024