Nebivolol is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in water, and almost insoluble in chloroform, ethanol, and ether.

The chemical name for the active ingredient in BYSTOLIC (nebivolol) Tablets is \((1RS,1'RS)-1,1'-[2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl]-2,2'-iminodiethanol hydrochloride\). Nebivolol is a racemate composed of d-nebivolol and l-nebivolol with the stereochemical designations (S)-nebivolol and (R)-nebivolol, respectively. Nebivolol's molecular formula is \(\text{C}_{22}\text{H}_{26}\text{F}_2\text{N}_2\text{O}_{8}\text{HCl}\) with the following structural formulas:

\[
\begin{align*}
\text{HCl} & \quad \text{HCl} \\
\text{SSRR} & \quad \text{SR-d-nebivolol hydrochloride} \\
\text{RSSS} & \quad \text{SR-l-nebivolol hydrochloride} \\
\text{MW:} & \quad 441.90 \text{g/mol}
\end{align*}
\]

**Bronchopulmonary Disease**

In general, bronchopulmonary diseases should not receive β-blockers.

**Anesthesia and Major Surgery**

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

**Use with CYP2D6 inhibitors**

BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolic clearance. Since BYSTOLIC is not extensively metabolized, its bioavailability is not significantly affected by the concomitant use of CYP2D6 inhibitors.

BYSTOLIC should be used with caution in patients with severe hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic impairment.

**Risk of Anaphylactic Reactions**

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

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

**Special Populations**

**Diabetes and Hypoglycemia**

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

**Thyrotoxicosis**

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

**Non-dihydropyridine Calcium Channel Blockers**

Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the diltiazem type, caution should be exercised in these patients.

**β-blockers**

The combined use of β-blockers and calcium channel blockers of the diltiazem type is contraindicated. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

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The rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group. In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol compared to placebo. 

In a 24-month study in Wistar rats receiving doses of nebivolol of 2.5, 10 and 40 mg/kg (equivalent to 0.2, 0.8, 2.4, and 10 times the maximally recommended human dose), co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an intact LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man. Nebivolol caused prolonged gestation and dystocia at doses ≥5 mg/kg in rats (1.2 times the MRHD). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced in rats with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival rate. These effects occurred only when nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD). 

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 (5 and 10 times the MRHD), and small reversible delays in internal and throracic ossification associated with the reduced fetal body weights and a small increase in resorption at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which neonates was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD). 

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In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12–19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved. 

The patient should be given a copy of the Patient Information Guide (see PRECAUTIONS, Geriatric Use). 

DOSAGE AND ADMINISTRATION 

The dose of BYSTOLIC should be individualized to the needs of the patient. For most patients, the recommended starting dose is 2.5 mg once daily: upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients monitoring dialysis (see CLINICAL PHARMACOLOGY, Special Populations). 

In severely hypertensive patients, the recommended initial dose is 2.5 mg once daily: upward titration should be performed cautiously if needed. The dose can be increased at 1–2 week intervals up to 10 mg. A more frequent dosing regimen is unlikely to be beneficial. 

A randomized, double-blind, active- and placebo-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on maternal function, uterine hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no significant effect on ACTH-stimulated mean cortisol AUC0-120 min, serum LH, or serum total testosterone levels. 

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