The first and only beta blocker (BB) + angiotensin receptor blocker (ARB) fixed-dose combination therapy[1]

NEW

Byvalson™

(nebivolol and valsartan) tablets

5 mg/80 mg

Indications and Usage

BYVALSON is indicated for the treatment of hypertension, to lower blood pressure. BYVALSON may be used alone or in combination with other antihypertensive agents. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. There are no controlled trials demonstrating risk reduction with BYVALSON, but at least one pharmacologically similar drug has demonstrated such benefits.

Important Safety Information

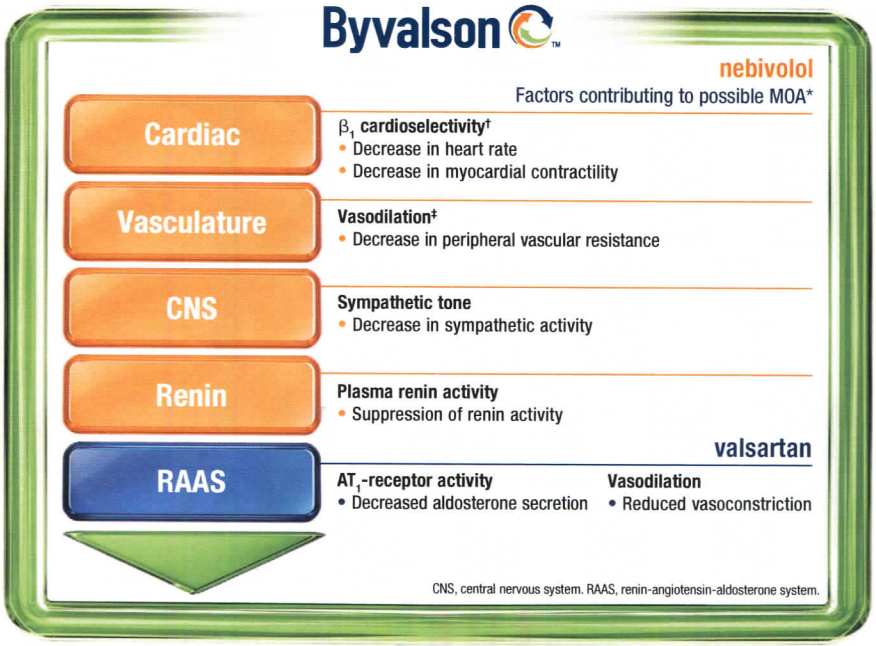
WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue BYVALSON as soon as possible.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.**

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Mechanism of Action

BYVALSON combines the mechanisms of action (MOAs) of nebivolol and valsartan[1]



***The mechanism of action of the antihypertensive response of nebivolol has not been definitively established.**

†In extensive metabolizers (most of the population) and at doses ≤10 mg, the nebivolol component of BYVALSON is preferentially β_1 selective.

‡At clinically relevant doses, the nebivolol component of BYVALSON does not demonstrate α_1-adrenergic-receptor blockade activity.

Important Safety Information

Contraindications

BYVALSON is contraindicated in the following conditions: severe bradycardia, heart block greater than first degree, patients with cardiogenic shock, decompensated cardiac failure, Sick sinus syndrome (unless a permanent pacemaker is in place), patients with severe hepatic impairment (Child-Pugh >B), and patients who are hypersensitive to any component of this product. Do not co-administer aliskiren with BYVALSON in patients with diabetes.

Warnings and Precautions

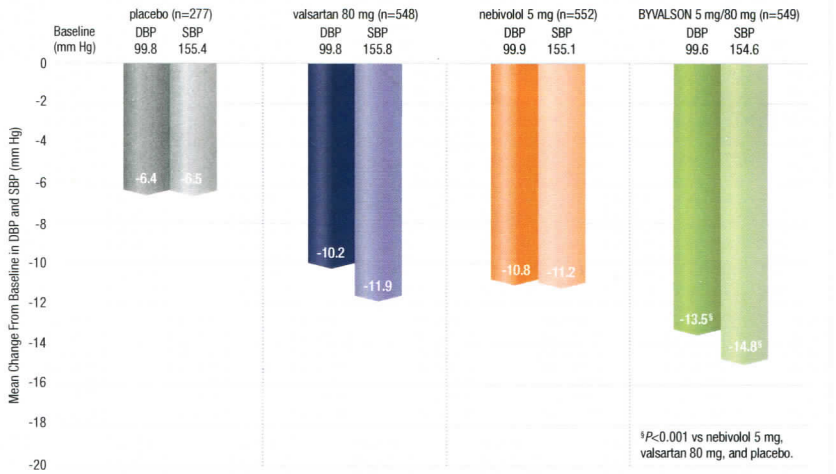
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, discontinue BYVALSON as soon as possible.

In patients with an activated renin-angiotensin-aldosterone system, symptomatic hypotension may occur in patients receiving BYVALSON. Correct these conditions prior to administration of BYVALSON, or start the treatment under close medical supervision. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Significant Blood Pressure Reductions

Significant blood pressure reductions with BYVALSON vs monotherapy at Week 4[1,2]

4-Week Reductions in Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP) From Baseline



Study Design: Results from an 8-week, multicenter, placebo-controlled, double-blind, dose-escalating trial in 4161 patients with Stage 1 or Stage 2 hypertension. Patients were randomized to receive valsartan 80 mg or 160 mg, nebivolol 5 mg or 20 mg, BYVALSON 5 mg/80 mg, 5 mg/160 mg, or 10 mg/160 mg, or placebo once daily. After 4 weeks, patients randomized to active treatment were force-titrated to double their previous doses and were treated for an additional 4 weeks. The primary efficacy assessment was change from baseline to the end of double-blind treatment phase at Week 8 in seated DBP at trough. Mean blood pressure at baseline: DBP, 100 mm Hg; SBP, 155 mm Hg. The last-observation-carried-forward method was used to calculate missing treatment values.[1,2]

Treatment with BYVALSON 5 mg/80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in SBP and DBP blood pressure of -8.3 and -7.2 mm Hg, respectively[1]

- BYVALSON was studied in patients with Stage I and II hypertension[1]
  - — Demographics in the registration trial included patients who were approximately 56% male, 85% Caucasian, 10% Black, 41% Hispanic, 15% diabetic, and 9% 65 years of age or older
- BYVALSON lowered blood pressure over the full 24-hour dosing interval based on Ambulatory Blood Pressure Monitoring assessments[1]
- DBP and SBP reductions seen as early as Week 2 with BYVALSON[1]
- Mean sitting pulse rate at trough was reduced in patients treated with BYVALSON[1,2]
  - — BYVALSON 5 mg/80 mg had a mean reduction in pulse rate of -9.7 bpm vs -2.6 bpm in placebo

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Adverse Events Profile[1]

In the 4-week study period of the registration trial[1]...

- The overall incidence of adverse events with BYVALSON 5 mg/80 mg was similar to that of placebo and the individual components during the 4-week study period
- Discontinuation rates due to an adverse event were 2.0% with BYVALSON 5 mg/80 mg vs 3.2% with placebo
- In patients receiving monotherapy with nebivolol 5 mg or valsartan 80 mg, the discontinuation rate was approximately 1%

Important Safety Information (continued)

Warnings and Precautions (continued)

Do not abruptly discontinue BYVALSON 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 ß-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. As with other β-blocker therapies, when discontinuation of BYVALSON is planned, carefully observe and advise patients to minimize physical activity. Taper nebivolol using monotherapy over 1 to 2 weeks when possible. If the angina worsens re-start nebivolol promptly, at least temporarily.

Worsening heart failure or fluid retention may occur during nebivolol therapy because of its β-blocking effects. Consider diuretic therapy and treat heart failure appropriately, according to current guidelines.

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

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.

β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.

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.

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor heart rate and blood pressure in patients treated concomitantly with these agents.

Getting started on BYVALSON

Convenient once-daily dosing[1]

Rx
BYVALSON
5 mg/80 mg
#30
Sig: 1 tab once daily
Refills: 5

Savings for patients

BYVALSON™ SAVINGS CARD

MOST ELIGIBLE PATIENTS PAY AS LITTLE AS **$30** PER 30-DAY PRESCRIPTION

This card requires activation. Visit www.byvalsonsavings.com or call 1.855.661.4491

RxBIN: **637765**
RxPCN: **CRX**
RxGRP: **COMP2**
RxID: **XXXXXXXXX**

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Important Safety Information (continued)

Warnings and Precautions (continued)

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system may be at particular risk of developing acute renal failure on valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on valsartan.

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

In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.

In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. Discontinuation of BYVALSON may be required.

Drug Interactions

Avoid concomitant use with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc).

Do not use with other beta-blockers. Monitor patients receiving catecholamine-depleting drugs (e.g. reserpine or guanethidine) or clonidine as they may produce excessive reduction of sympathetic activity. Discontinue nebivolol for several days before the gradual tapering of clonidine.

Concomitant use with digitalis glycosides can increase the risk of bradycardia. Monitor for bradycardia.

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The first and only BB + ARB fixed-dose combination therapy[1]

Nebivolol and valsartan are now combined in one pill to provide significant blood pressure reductions with a low incidence of side effects.

- BYVALSON combines the MOAs of nebivolol and valsartan[1]
- Significant blood pressure reductions vs monotherapy alone[1]
- Maximum antihypertensive effects are attained within 2 to 4 weeks[1]
- The overall incidence of adverse events with BYVALSON 5 mg/80 mg was similar to that of placebo and the individual components during a 4-week placebo-controlled trial[1]
- Discontinuation rates due to adverse events were 2% in patients treated with BYVALSON vs 3.2% in placebo-treated patients[1]

Important Safety Information (continued)

WARNING: FETAL TOXICITY

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Drug Interactions (continued)

Nebivolol can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the verapamil- and diltiazem-type) or antiarrhythmic agents. Monitor for effects on heart rate and cardiac conduction.

Concomitant use with other agents that block the renin-angiotensin system, potassium-sparing diuretics, potassium supplements or salt substitutes, or other agents that may increase potassium levels may result in hyperkalemia. Monitor serum potassium.

Co-administration with NSAIDs may result in deterioration of renal function, including possible acute renal failure, and loss of antihypertensive effect. Monitor renal function.

Concomitant use with ACE inhibitors or with aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Monitor blood pressure, renal function and electrolytes. Avoid concomitant use with aliskiren in patients with renal impairment.

Increases in lithium concentrations and toxicity have been reported during concomitant administration with lithium. Monitor serum lithium levels.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

References: 1. BYVALSON [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2016.
2. Data on file. Forest Laboratories, LLC.

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