

BYVALSON- nebivolol hydrochloride and valsartan tablet, film coated
Allergan, Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BYVALSON safely and effectively. See full prescribing information for BYVALSON.

BYVALSON (nebivolol and valsartan) tablets, for oral use

Initial U.S. Approval: 2016

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- When pregnancy is detected, discontinue BYVALSON as soon as possible (5.1, 8.1)
- Drugs, including BYVALSON, that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1)

INDICATIONS AND USAGE

BYVALSON is a beta adrenergic blocker and an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

DOSAGE AND ADMINISTRATION

- As initial therapy and in patients not adequately controlled on valsartan 80 mg or nebivolol up to and including 10 mg, the recommended dose is 5 mg/ 80 mg taken orally once daily. (2)
- Maximum antihypertensive effects are attained within 2 to 4 weeks. (2)
- BYVALSON may be substituted for its components in patients already receiving 5 mg nebivolol and 80 mg valsartan. (2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg/ 80 mg (3)

CONTRAINDICATIONS

- Severe bradycardia (4)
- Heart block greater than first degree (4)
- Patients with cardiogenic shock (4)
- Decompensated cardiac failure (4)
- Sick sinus syndrome (unless a permanent pacemaker is in place) (4)
- Patients with severe hepatic impairment (Child-Pugh >B) (4)
- Hypersensitivity to any component of this product (4)
- Do not co-administer aliskiren with BYVALSON in patients with diabetes. (4)

WARNINGS AND PRECAUTIONS

- Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue. (5.3)
- Diabetes: Monitor glucose as β -blockers may mask symptoms of hypoglycemia. (5.7)
- Monitor renal function and potassium in susceptible patients. (5.11)

ADVERSE REACTIONS

No adverse reactions were observed more frequently on BYVALSON than on placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2D6 enzyme inhibitors increase nebivolol levels. (7)
- Reserpine or clonidine may produce excessive reduction of sympathetic activity. (7)
- Digitalis glycosides increase the risk of bradycardia. (7)
- Verapamil- or diltiazem-type calcium channel blockers may cause excessive reductions in heart rate, blood pressure, and cardiac contractility. (7)
- Potassium sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium. (7)
- NSAID use may lead to increased risk of renal impairment and loss of antihypertensive effect. (7)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia. (7)

- Lithium: Increases in serum lithium concentrations and lithium toxicity (7)

-----USE IN SPECIFIC POPULATIONS -----

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FETAL TOXICITY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Fetal Toxicity
- 5.2 Hypotension
- 5.3 Abrupt Cessation of Therapy
- 5.4 Cardiac Failure
- 5.5 Bronchospastic Diseases
- 5.6 Anesthesia and Major Surgery
- 5.7 Diabetes and Hypoglycemia
- 5.8 Thyrotoxicosis
- 5.9 Peripheral Vascular Disease
- 5.10 Non-dihydropyridine Calcium Channel Blockers
- 5.11 Impaired Renal Function
- 5.12 Risk of Anaphylactic Reactions
- 5.13 Pheochromocytoma
- 5.14 Hyperkalemia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue BYVALSON as soon as possible (5.1, 8.1).**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1, 8.1).**

1 INDICATIONS AND USAGE

BYVALSON is indicated for the treatment of hypertension, to lower blood pressure.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including the β -blocker class to which nebivolol principally belongs and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with BYVALSON.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mm Hg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

BYVALSON may be used alone or in combination with other antihypertensive agents.

2 DOSAGE AND ADMINISTRATION

As initial therapy and in patients not adequately controlled on valsartan 80 mg or nebivolol up to and including 10 mg, the recommended dose of BYVALSON is one tablet, 5 mg/ 80 mg (nebivolol/valsartan) taken orally once daily. Maximum antihypertensive effects are attained within 2 to 4

weeks. Increasing the dose of BYVALSON does not result in any meaningful further blood pressure reduction [see *Clinical Studies (14)*].

BYVALSON may be substituted for its components in patients already receiving 5 mg nebivolol and 80 mg valsartan.

3 DOSAGE FORMS AND STRENGTHS

BYVALSON is available as a purple, capsule shaped, film-coated tablet with FL1 debossed on one side containing 5 mg of nebivolol and 80 mg of valsartan.

4 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)
- Patients who are hypersensitive to any component of this product.
- Do not co-administer aliskiren with BYVALSON in patients with diabetes [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Valsartan

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. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue BYVALSON as soon as possible [see *Use in Specific Populations (8.1)*].

5.2 Hypotension

In patients with an activated renin-angiotensin-aldosterone system, such as volume- and/or salt-depleted patients (e.g., those receiving high doses of diuretics), 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.

5.3 Abrupt Cessation of Therapy

Nebivolol

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 β -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.

5.4 Cardiac Failure

Nebivolol

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.

5.5 Bronchospastic Diseases

Nebivolol

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

5.6 Anesthesia and Major Surgery

Nebivolol

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.

5.7 Diabetes and Hypoglycemia

Nebivolol

β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.

5.8 Thyrotoxicosis

Nebivolol

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.

5.9 Peripheral Vascular Disease

Nebivolol

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

5.10 Non-dihydropyridine Calcium Channel Blockers

Nebivolol

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.

5.11 Impaired Renal Function

Valsartan

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 (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) 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 [see *Drug Interactions (7)*].

5.12 Risk of Anaphylactic Reactions

Nebivolol

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

5.13 Pheochromocytoma

Nebivolol

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

5.14 Hyperkalemia

Valsartan

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.

6 ADVERSE REACTIONS

The following serious adverse reactions are included in more detail in the Warnings and Precautions section of the label:

- Hypotension [see *Warnings and Precautions (5.2)*]
- Hyperkalemia [see *Warnings and Precautions (5.14)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BYVALSON

BYVALSON has been evaluated for safety in patients with hypertension. A total of 1,664 patients received at least 1 dose of a fixed-dose combination of nebivolol/valsartan in an 8-week trial. A total of 807 patients received at least 1 dose of nebivolol and valsartan in an open-label safety study; of these, 621 patients completed 180 days and 476 patients completed 360 days of open-label treatment with nebivolol and valsartan.

The safety of the 5 mg/ 80 mg dose of nebivolol/valsartan was evaluated during the first 4 weeks of an 8-week placebo-controlled trial. During the 4 week period, the overall incidence of adverse events on therapy with BYVALSON 5 mg/ 80 mg was similar to placebo and the individual components (nebivolol 5 mg and valsartan 80 mg). Discontinuation of therapy due to a clinical adverse event occurred in 2.0% of patients treated with BYVALSON 5 mg/ 80 mg versus 3.2% of patients given placebo and

approximately 1% of patients given nebivolol 5 mg or valsartan 80 mg as monotherapy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of either nebivolol or valsartan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nebivolol

The following adverse reactions have been reported in post-marketing experience:

Cardiac: atrioventricular block (both second and third degree), myocardial infarction

Central Nervous System: somnolence, syncope, vertigo

Circulatory: Raynaud's phenomenon, peripheral ischemia/ Claudication, thrombocytopenia

Dermatologic: pruritus, psoriasis, various rashes and skin disorders

Digestive: vomiting

Hepatic: Abnormal hepatic function (including increased AST, ALT and bilirubin)

Hypersensitivity: hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema)

Renal: acute renal failure

Respiratory: acute pulmonary edema, bronchospasm

Sexual Dysfunction: erectile dysfunction

Valsartan

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Angioedema.

Digestive: Elevated liver enzymes, hepatitis

Renal: Impaired renal function, renal failure

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia, bullous dermatitis

Blood and Lymphatic: thrombocytopenia

Vascular: Vasculitis

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with BYVALSON and other drugs. Studies with the individual nebivolol and valsartan components are described below.

Nebivolol

CYP2D6 Inhibitors: Avoid concomitant use of nebivolol with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) [see *Clinical Pharmacology* (12.3)].

Hypotensive Agents: Do not use nebivolol with other β -blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β -blocking action of nebivolol may produce excessive reduction of sympathetic activity. In patients who are receiving nebivolol and clonidine, discontinue nebivolol for several days before the gradual tapering of clonidine.

Digitalis Glycosides: Concomitant use can increase the risk of bradycardia. Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease heart rate. Monitor for bradycardia.

Calcium Channel Blockers: Nebivolol can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide. Monitor for effects on heart rate and cardiac conduction.

Valsartan

Agents Increasing Serum Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other agents that may increase potassium levels (e.g., heparin) may result in hyperkalemia. Monitor serum potassium in such patients.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Use with Other Renin Angiotensin System inhibitors: Use of angiotensin receptor blockers 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. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on valsartan and ACE inhibitors or aliskiren.

Do not co-administer aliskiren with BYVALSON in patients with diabetes. Avoid use of aliskiren with BYVALSON in patients with renal impairment (GFR <60 mL/min).

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium angiotensin II receptor antagonists, including valsartan. Monitor serum lithium levels during concomitant use.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

BYVALSON can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to angiotensin receptor blockers use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Studies in rats and rabbits with valsartan showed fetotoxicity only at maternally toxic doses [see Data]. Embryo-fetal and perinatal lethality have been observed when nebivolol was given to pregnant rats during organogenesis at doses approximately equivalent to the MRHD. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan. When pregnancy is detected, discontinue BYVALSON as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Nebivolol

Neonates of women with hypertension, who are treated with beta-blockers during pregnancy, may be at increased risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Observe newborns for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Valsartan

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia and skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

BYVALSON

In patients taking BYVALSON during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to BYVALSON for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occur in neonates with a history of *in utero* exposure to BYVALSON, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and substituting for disordered renal function.

Data

Animal Data

No reproductive animal toxicity studies have been conducted with the combination of nebivolol and valsartan. Reproductive animal toxicity studies have been conducted for nebivolol and valsartan alone.

Nebivolol

Nebivolol was shown to increase embryo-fetal and perinatal lethality in rats at approximately 1.2 times the maximum recommended human dose (MRHD) or 40 mg/day on a mg/m² basis. 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 (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. These events occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), 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 (10 times the MRHD).

No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m² basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

8.2 Lactation

Risk Summary

There is no information regarding the presence of BYVALSON or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Nebivolol and valsartan are present in rat milk [see Data]. Because of the potential for β -blockers to produce serious adverse reactions in nursing infants, especially bradycardia, and the potential for valsartan to affect postnatal renal development in nursing infants, advise a nursing woman not to breastfeed during treatment with BYVALSON.

Data

In lactating rats, maximum milk levels of unchanged nebivolol were observed at 4 hours after single and repeat doses of 2.5 mg/kg/day. The daily dose (mg/kg body weight) ingested by a rat pup is 0.3% of the dam dose for unchanged nebivolol. For valsartan, drug was detected in the milk of lactating rats 15 minutes after administration of a 3 mg/kg dose.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

BYVALSON

In clinical trials of BYVALSON, 204 (8.3%) patients who were treated with BYVALSON were \geq 65 years and 16 (0.6%) were \geq 75 years.

No overall differences in safety or effectiveness were observed between elderly patients and younger patients, and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Safety and effectiveness of BYVALSON in patients with moderate and severe renal impairment (creatinine clearance [CrCl] \leq 60 mL/min) have not been studied. No dosage adjustment is required for patients with mild or moderate renal impairment.

BYVALSON is not recommended as initial treatment in patients with severe renal impairment, because the recommended starting dose of nebivolol in this population, 2.5 mg once daily, is lower than the dose of nebivolol contained in BYVALSON.

8.7 Hepatic Impairment

There are no studies of BYVALSON in patients with hepatic insufficiency. No initial dosage adjustment is required for patients with mild hepatic impairment.

BYVALSON is not recommended as initial treatment in patients with moderate hepatic impairment, because the recommended starting dose of nebivolol, 2.5 mg once daily, is not available.

BYVALSON is not recommended for use in patients with severe hepatic impairment [see *Contraindications (4)*].

10 OVERDOSAGE

Nebivolol

In clinical trials and worldwide postmarketing experience there were reports of nebivolol overdose. The most common signs and symptoms associated with nebivolol overdose are bradycardia and hypotension. Other important adverse reactions reported with nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β -blocker overdose include bronchospasm and heart 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 hyperhidrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

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

Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases, consider the use of inotropic and vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β_2 -agonist and/or aminophylline.

Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours.

Valsartan

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats

and up to 1,000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

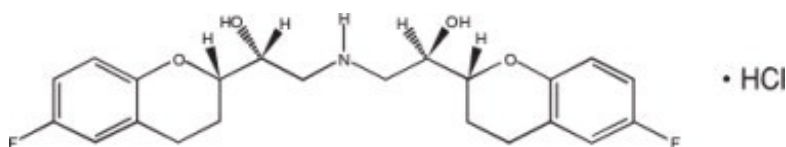
11 DESCRIPTION

BYVALSON

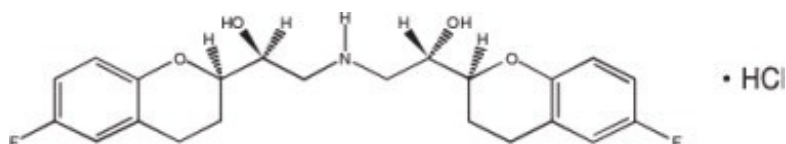
BYVALSONTM is available as tablets for oral administration. Each tablet contains 5.45 mg of nebivolol hydrochloride, which is equivalent to 5 mg of nebivolol free base, and 80 mg of valsartan. The inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, copovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, talc, ferric oxide, hypromellose, polysorbate 80, and Opadry[®] II Purple film-coat. The Opadry[®] II is made of polyvinyl alcohol-part hydrolyzed, titanium dioxide, talc, polyethylene glycol, iron oxide red, and ferrosoferric oxide/black iron oxide.

Nebivolol

BYVALSONTM tablets contain nebivolol hydrochloride as one of two active ingredients. Nebivolol hydrochloride is chemically described as (1*RS*,1'*RS*)-1,1'-[(2*RS*, 2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol hydrochloride is present as a racemic mixture of *d*-Nebivolol hydrochloride and *l*-Nebivolol hydrochloride with the stereochemical designations of [SRRR]-nebivolol hydrochloride and [RSSS]-nebivolol hydrochloride, respectively. The molecular formula of both the forms is C₂₂H₂₅F₂NO₄•HCl and their structural formulas are provided below:



(SRRR) - or *d*-nebivolol hydrochloride



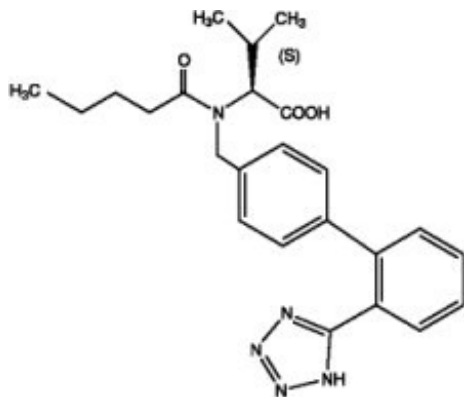
(RSSS) - or *l*-nebivolol hydrochloride

MW: 441.90 g/mol

Nebivolol hydrochloride is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

Valsartan

Valsartan, the other active ingredient in BYVALSON, is chemically described as *N*-(1-Oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-*L*-valine. Its molecular formula is C₂₄H₂₉N₅O₃, its molecular weight is 435.52, and its structural formula is:



Valsartan is a white or almost white fine powder. It is freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride, and practically insoluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nebivolol

Nebivolol is a β -adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 - and β_2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, nebivolol does not demonstrate α_1 -adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β -blocking activity.

The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) decreased sympathetic activity, (4) suppression of renin activity, and (5) vasodilation and decreased peripheral vascular resistance.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one- 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

BYVALSON

In a placebo-controlled hypertensive patient study, valsartan was associated with an increase in PRA (60-73% increase) whereas nebivolol was associated with a 51-65% reduction in PRA. Nebivolol in combination with valsartan reduced PRA (3-39% reduction). Nebivolol, valsartan, and BYVALSON decreased plasma aldosterone levels. Administration of BYVALSON to patients with essential hypertension results in a significant reduction of sitting, and standing diastolic and systolic blood pressure. Decreases in pulse rate from baseline were also observed in the BYVALSON and nebivolol treatment groups.

12.3 Pharmacokinetics

Absorption and Distribution

BYVALSON

Following oral administration of BYVALSON, peak plasma nebivolol concentrations are reached approximately 1 to 6 hours post-dosing. Peak plasma valsartan concentrations are reached in approximately 2 to 4 hours post-dosing. The rate and extent of absorption of nebivolol and valsartan from BYVALSON are the same as when administered separately. Food had a minor impact on the pharmacokinetics of nebivolol, nebivolol glucuronides and valsartan. BYVALSON may be administered without regard to meals. BYVALSON demonstrates dose-proportional increases in exposure over the clinical dosing range.

Nebivolol

Exposure to *l*-nebivolol is higher than to *d*-nebivolol but *l*-nebivolol contributes little to the drug's β -blocking activity as *d*-nebivolol's β -receptor affinity is > 1,000-fold higher than *l*-nebivolol.

For the same dose, CYP2D6 poor metabolizers (PMs) attain a 5-fold higher C_{max} and 10-fold higher AUC of nebivolol than do extensive metabolizers (EMs). With repeated once-daily dosing of BYVALSON, nebivolol accumulates about 1.2-fold in EMs and 3-fold in PMs, respectively; valsartan accumulates about 1.5-fold.

The *in vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Valsartan

The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Metabolism and Elimination

Nebivolol

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. *d*-Nebivolol, has an effective half-life of about 12 hours in CYP2D6 EMs, and 19 hours in PMs and exposure to *d*-nebivolol is substantially increased in PMs. The difference in *d*-nebivolol exposure between EMs and PMs is not considered important because nebivolol metabolites, including the hydroxyl metabolite and glucuronides (the prominent circulating metabolites) contribute to the pharmacologic activity.

After a single oral administration of ^{14}C -nebivolol, 38% of the dose was recovered in urine and 44% in

feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Valsartan

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl-4-hydroxy valsartan. *In vitro* metabolism studies involving recombinant CYP450 enzymes indicated that the CYP2C9 isozyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP450 isozymes at clinically relevant concentrations. CYP450 mediated drug interactions between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Specific Populations

Hepatic Impairment

Nebivolol

d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). No formal studies have been performed in patients with severe hepatic impairment; nebivolol is contraindicated for these patients [*see Use in Specific Population (8.7)*].

Valsartan

On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease.

Renal Impairment

Nebivolol

The apparent clearance of nebivolol was unchanged following a single 5 mg dose of nebivolol in patients with mild renal impairment (CrCl 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate renal impairment (CrCl 30 to 50 mL/min, n=9), but clearance was reduced by 53% in patients with severe renal impairment (CrCl <30 mL/min, n=5). No studies have been conducted in patients on dialysis [*see Use in Specific Population (8.6)*].

Valsartan

There is no apparent correlation between renal function (measured by CrCl) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (CrCl <10 mL/min). Valsartan is not removed from the plasma by hemodialysis [*see Use in Specific Population (8.6)*].

Drug Interactions

Nebivolol

Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When nebivolol is co-administered with an inhibitor or an inducer of this enzyme, monitor patients closely and adjust the nebivolol dose according to blood pressure response. *In vitro* studies have demonstrated that at therapeutically relevant concentrations, *d*- and *l*-nebivolol do not inhibit any cytochrome P450 pathways.

Fluoxetine: Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior 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 [see Drug Interactions (7)].

Digoxin: Concomitant administration of nebivolol (10 mg once daily) and digoxin (0.25 mg once daily) for 10 days in 14 healthy adult individuals resulted in no significant changes in the pharmacokinetics of digoxin or nebivolol [see Drug Interactions (7)].

Warfarin: Administration of nebivolol (10 mg once daily for 10 days) led to no significant changes in the pharmacokinetics of nebivolol or R- or S-warfarin following a single 10 mg dose of warfarin. Similarly, nebivolol has no significant effects on the anticoagulant activity of warfarin, as assessed by Prothrombin time and INR profiles from 0 to 144 hours after a single 10 mg warfarin dose in 12 healthy adult volunteers.

Diuretics: 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).

Ramipril: Concomitant administration of nebivolol (10 mg once daily) and ramipril (5 mg once daily) for 10 days in 15 healthy adult volunteers produced no pharmacokinetic interactions.

Losartan: Concomitant administration of nebivolol (10 mg single dose) and losartan (50 mg single dose) in 20 healthy adult volunteers did not result in pharmacokinetic interactions.

Valsartan: Concomitant administration of nebivolol (20 mg once daily) and valsartan (320 mg once daily) in 30 healthy adult volunteers did not result in clinically significant pharmacokinetic interactions.

Histamine-2 Receptor Antagonists: 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.

Charcoal: The pharmacokinetics of nebivolol (10 mg single dose) were not affected by repeated co-administration (4, 8, 12, 16, 22, 28, 36, and 48 hours after nebivolol administration) of activated charcoal (Actidose-Aqua®).

Sildenafil: 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%). The effect on vital signs (e.g., pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Other Concomitant Medications: Utilizing population pharmacokinetic analyses using data derived from hypertensive patients, the following drugs are not expected to have an effect on the pharmacokinetics of nebivolol: acetaminophen, acetylsalicylic acid, atorvastatin, esomeprazole, ibuprofen, levothyroxine sodium, metformin, sildenafil, simvastatin, or tocopherol.

Protein Binding: No meaningful changes in the extent of *in vitro* binding of nebivolol to human plasma proteins were noted in the presence of high concentrations of diazepam, digoxin, diphenylhydantoin, enalapril, hydrochlorothiazide, imipramine, indomethacin, propranolol, sulfamethazine, tolbutamide, or warfarin. Additionally, nebivolol did not significantly alter the protein binding of the following drugs: diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with nebivolol, amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin.

Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a

substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nebivolol

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 at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m² basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5 mg/kg/day, 10 mg/kg/day and 40 mg/kg/day (equivalent to 0.6, 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 indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing 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 serum cortisol AUC_{0-120 min}, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥ 40 mg/kg/day (10 and 5 times the MRHD, respectively). 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.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, *in vitro* mouse lymphoma TK⁺/-, *in vitro* human peripheral lymphocyte chromosome aberration, *in vivo* *Drosophila melanogaster* sex-linked recessive lethal, and *in vivo* mouse bone marrow micronucleus tests).

Valsartan

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

14 CLINICAL STUDIES

BYVALSON was studied in a Phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study in 4,161 patients with Stage 1 or 2 hypertension. Patients were initially randomized to 1 of 8 treatment groups including: 3 fixed-dose combinations (FDC) of nebivolol and valsartan (5 mg/ 80 mg, 5 mg/ 160 mg, 10 mg/ 160 mg), nebivolol monotherapy (5 mg, 20 mg), valsartan monotherapy (80 mg, 160

mg), or placebo. After 4 weeks of treatment, all doses were doubled in the FDC groups (to 10 mg/ 160 mg, 10 mg/ 320 mg, and 20 mg/ 320 mg), nebivolol monotherapy groups (to 10 mg, 40 mg), and valsartan monotherapy groups (to 160 mg, 320 mg).

Mean baseline systolic blood pressure was 155 mm Hg and mean baseline diastolic blood pressure was 100 mm Hg. Approximately 56% of patients were male, 85% were Caucasian, 10% were Black, 41% were Hispanic, 15% were diabetic, and 9% were 65 years of age or older.

Treatment with BYVALSON 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in systolic (SBP) and diastolic (DBP) blood pressure of -8.3 and -7.2 mmHg, respectively. Treatment with BYVALSON 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone ($p < 0.0001$ for both SBP and DBP) or valsartan 80 mg, alone ($p = 0.0007$ for SBP and $p < 0.0001$ for DBP).

Table 1. Placebo-Corrected Change from Baseline in Blood Pressure at Week 4

<i>Change From Baseline</i>	<i>Byvalson 5mg/ 80mg mmHg (95% CI)</i>	<i>Valsartan 80 mg mmHg (95% CI)</i>	<i>Valsartan 160 mg mmHg (95% CI)</i>	<i>Nebivolol 5 mg mmHg (95% CI)</i>	<i>Nebivolol 20 mg mmHg (95% CI)</i>	<i>Byvalson 5mg/160mg mmHg (95% CI)</i>	<i>Byvalson 10mg/160mg mmHg (95% CI)</i>
DBP	-7.2 (-8.4, -5.9)	-3.9 (-5.1, -2.6)	-4.6 (-5.8, -3.3)	-4.4 (-5.7, -3.2)	-7.5 (-8.7, -6.2)	-7.4 (-8.7, -6.1)	-7.9 (-9.2, -6.6)
SBP	-8.3 (-10.3, -6.3)	-5.4 (-7.4, -3.4)	-7.5 (-9.5, -5.4)	-4.7 (-6.7, -2.7)	-7.4 (-9.4, -5.4)	-8.8 (-10.9, -6.8)	-9.0 (-11.0, -7.0)

The antihypertensive effect of valsartan and nebivolol was independent of age and gender in clinical trials evaluating the antihypertensive effect of nebivolol and valsartan administered as monotherapies. Antihypertensive drugs that affect the renin-angiotensin system such as angiotensin converting enzyme inhibitors and angiotensin-II blockers have generally been found to be less effective in low-renin hypertensive patients (frequently Blacks) as compared to high-renin hypertensive patients (frequently whites). Although the effectiveness of nebivolol as a monotherapy has been established in Blacks, as a monotherapy, the magnitude of nebivolol's effect in Blacks was somewhat less than in Caucasians.

The blood pressure lowering effect of BYVALSON was maintained over the 24-hour dosing interval based on Ambulatory Blood Pressure Monitoring (ABPM) assessments. Mean heart rate (assessed as a part of 24-hour measurements or at sitting-trough in the 8-week or the 52-week studies) was reduced in patients groups treated with BYVALSON.

16 HOW SUPPLIED/STORAGE AND HANDLING

BYVALSON tablets are supplied in the following strengths and package configurations:

BYVALSON				
Tablet Strength	Package Configuration	NDC #	Tablet Color/Shape	Tablet Marking
5 mg nebivolol/ 80 mg valsartan per tablet	Bottle of 30	0023-5874-30	Purple / capsule shaped	FL1 on one side
	Bottle of 90	0023-5874-90		

Store at 20° to 25°C (68° to 77°F) [see USP for Controlled Room Temperature].

Dispense in a tightly closed container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to notify their healthcare provider with a known or suspected pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

Lactation

Advise women not to breastfeed during treatment with BYVALSON [see Use in Specific Populations (8.2)].

Symptomatic Hypotension

Advise patients that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell patients that if syncope occurs to discontinue BYVALSON until the physician has been consulted.

Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia

Advise patients not to use salt substitutes containing potassium without consulting their physician.

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Allergan USA, Inc.
Irvine, CA 92612

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<p style="text-align: center;">PATIENT INFORMATION BYVALSON (bye-VAL-son) (nebivolol/valsartan) tablets</p>

<p>What is the most important information I should know about BYVALSON?</p>

- | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• BYVALSON can cause harm or death to your unborn baby.• Talk to your healthcare provider about other ways to lower your blood pressure if you plan to become pregnant.• If you become pregnant while taking BYVALSON, tell your healthcare provider right away. Your healthcare provider may switch you to a different medicine to treat your high blood pressure. |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

<p>What is BYVALSON?</p>

<p>BYVALSON is a prescription medicine that contains nebivolol, a beta-blocker and valsartan, an angiotensin receptor blocker (ARB). BYVALSON is used to treat high blood pressure (hypertension) in adults.</p>

<p>It is not known if BYVALSON is safe and effective in children.</p>

<p>Who should not take BYVALSON?</p>

<p>Do not take BYVALSON if you:</p>

- | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• have a very low heart rate (severe bradycardia)• have heart block that is greater than the 1st degree• have symptoms of heart failure that recently worsened and you were hospitalized or require certain |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

medicines to help with your blood circulation (decompensated cardiac failure)

- have a certain heart condition called sick sinus syndrome, **unless** you have a permanent pacemaker
- have severe liver damage
- are allergic to nebivolol, valsartan, or any of the ingredients in BYVALSON. See the end of this Patient Information leaflet for a complete list of ingredients in BYVALSON.
- are taking a prescription medicine called aliskerin **and** you have diabetes

What should I tell my healthcare provider before taking BYVALSON?

Before taking BYVALSON, tell your healthcare provider about all of your medical conditions, including if you:

- have low blood pressure (hypotension)
- have heart problems
- have asthma, trouble breathing or other lung problems. BYVALSON is not recommended for use in patients with lung problems.
- plan to have surgery with general anesthesia
- have diabetes and take medicine to help control your blood sugar
- have thyroid problems
- have problems with decreased blood flow to your feet and legs (peripheral vascular disease)
- have kidney problems
- have liver problems
- have or have had allergies
- have a tumor on your adrenal gland called pheochromocytoma
- are pregnant or plan to become pregnant. See “**What is the most important information I should know about BYVALSON?**”
- are breastfeeding or plan to breastfeed. It is not known if BYVALSON passes into your breast milk. You should not breastfeed if you take BYVALSON.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking BYVALSON with certain other medicines can affect each other and cause serious side effects.

Especially tell your healthcare provider if you take:

- other medicines for high blood pressure or heart problems
- water pills (diuretics)
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium. Your healthcare provider may do certain tests to check your potassium blood level while you take BYVALSON.
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- an antibiotic called rifampin
- an organ transplant rejection medicine called cyclosporine
- fluoxetine
- medicines used to treat Human Immunodeficiency Virus (HIV) that contain ritonavir
- lithium

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take BYVALSON?

- Take BYVALSON exactly as your healthcare provider tells you. Your healthcare provider will tell you how much BYVALSON to take and when to take it.
- **Do not suddenly stop taking BYVALSON.** Stopping BYVALSON suddenly may cause you to have chest pain or a heart attack. Your healthcare provider may slowly lower your dose before you

stop taking BYVALSON.

- Take BYVALSON with or without food.
- If you take too much BYVALSON, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of BYVALSON?

BYVALSON may cause serious side effects, including:

- See “**What is the most important information I should know about BYVALSON?**”
- **Low blood pressure (hypotension) is most likely to happen if you also:**
 - take water pills (diuretics)
 - are on a low salt diet
 - are on kidney dialysis
 - have heart problems
 - have vomiting or diarrhea

Stop taking BYVALSON, lie down and call your healthcare provider right away if you feel faint or dizzy.

- **Worsening of chest pain (angina) or a heart attack (myocardial infarction).** See “**How should I take BYVALSON?**”.
- **If you have diabetes,** BYVALSON may hide signs of low blood sugar, such as fast heartbeat.
- **Worsening of heart failure.** If you suddenly develop shortness of breath, increased swelling of feet or legs, or gain more than 5 pounds quickly contact your doctor right away.
- **If you have an overactive thyroid gland (hyperthyroidism),** BYVALSON may hide signs of too much thyroid hormone in your blood, such as a fast heartbeat. If you stop taking BYVALSON suddenly, your symptoms of having too much thyroid hormone in your blood may become much worse, and could be life-threatening.
- **Worsening of blood flow to the feet and legs.** If you have problems with decreased blood flow to your feet and legs (peripheral vascular disease), your symptoms could get worse.
- **Kidney problems.** Some people with certain conditions may develop kidney problems and may need to stop treatment with BYVALSON. Call your healthcare provider if you get swelling in your feet, ankles, or hands, or unexplained weight gain.
- **Serious allergic reactions that can be life threatening.** Stop taking BYVALSON and get emergency medical help right away if you get any of these symptoms of a serious allergic reaction:
 - swelling of your face, lips, tongue, throat, arms, hands, legs, or feet
 - trouble breathing
 - stomach (abdomen) pain with or without nausea or vomiting
 - trouble swallowing
- **Increased amount of potassium in the blood.** Your healthcare provider may do certain tests to check your potassium blood level during your treatment with BYVALSON. Do not use salt substitutes containing potassium without first talking to your healthcare provider while taking BYVALSON.

The most common side effect of BYVALSON is:
slow heartbeat

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects with BYVALSON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BYVALSON?

- Store BYVALSON at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep BYVALSON in a tightly closed container.

Keep BYVALSON and all medicines out of the reach of children.

General information about the safe and effective use of BYVALSON.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BYVALSON for a condition for which it was not prescribed. Do not give BYVALSON to other people, even if they have the same symptoms that you have. It may harm them. This Patient Information leaflet summarizes the most important information about BYVALSON. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BYVALSON that is written for healthcare professionals.

What is high blood pressure (hypertension)?

Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too great. High blood pressure makes the heart work harder to pump blood through the body and causes damage to the blood vessels. BYVALSON can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure lower your chance of having a stroke or heart attack.

What are the ingredients in BYVALSON?

Active Ingredients: Nebivolol as hydrochloride salt and Valsartan

Inactive Ingredients: Lactose monohydrate, microcrystalline cellulose, copovidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, talc, ferric oxide, hypromellose, polysorbate 80, and Opadry® II Purple film-coat. The Opadry® II is made of polyvinyl alcohol-part hydrolyzed, titanium dioxide, talc, polyethylene glycol, iron oxide red, and ferrosferric oxide/black iron oxide.

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For more information, go to www.BYVALSON.com or call 1-800-433-8871.

This Patient Information has been approved by the U.S.
Food and Drug Administration

Issued: 06/2016

Principal Display Panel - 5 mg/80 mg Bottle Label

NDC 0023-5874-30

Byvalson™

(nebivolol and valsartan) tablets

5 mg/80 mg tablets

30 TABLETS Rx Only

Lot/Exp.



95874 NDC 0023-5874-30



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Byvalson 

(nebivolol and valsartan) tablets

5 mg/80 mg tablets

Each tablet contains: nebivolol hydrochloride and valsartan equivalent to 5 mg/80 mg nebivolol base/valsartan.

Usual dose: Take one tablet by mouth once daily.

Keep this and all drugs out of the reach of children.

Dispense in tightly closed containers.

Store at 20°C to 25°C (68°F to 77°F [See USP for Controlled Room Temperature]).

Made in Ireland

Distributed by Allergan USA, Inc.
Irvine, CA 92612 USA

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55505US10

30 TABLETS
Rx Only

BYVALSON

nebivolol hydrochloride and valsartan tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0023-5874
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
nebivolol hydrochloride (UNII: JGS34J7L9I) (nebivolol - UNII:030Y90569U)	nebivolol	5 mg
valsartan (UNII: 80M03YXJ7I) (valsartan - UNII:80M03YXJ7I)	valsartan	80 mg

Inactive Ingredients

Ingredient Name	Strength
lactose monohydrate (UNII: EWQ57Q8I5X)	
cellulose, microcrystalline (UNII: OP1R32D61U)	
copovidone (UNII: D9C330MD8B)	
croscarmellose sodium (UNII: M28OL1HH48)	
silicon dioxide (UNII: ETJ7Z6XBU4)	
magnesium stearate (UNII: 70097M6I30)	
talc (UNII: 7SEV7J4R1U)	
ferric oxide red (UNII: 1K09F3G675)	
hypromelloses (UNII: 3NXW29V3WO)	
polysorbate 80 (UNII: 6OZP39ZG8H)	
polyvinyl alcohol (UNII: 532B59J990)	
titanium dioxide (UNII: 15FIX9V2JP)	
polyethylene glycol 3350 (UNII: G2M7P15E5P)	

ferrosoferric oxide (UNII: XM0M87F357)

Product Characteristics

Color	purple (purple)	Score	no score
Shape	CAPSULE (CAPSULE)	Size	12mm
Flavor		Imprint Code	FL1
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0023-5874-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/03/2016	
2	NDC:0023-5874-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	06/03/2016	
3	NDC:0023-5874-32	5 in 1 TRAY	06/03/2016	
3	NDC:0023-5874-31	30 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:0023-5874-84	5 in 1 TRAY	06/03/2016	
4	NDC:0023-5874-07	7 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206302	06/03/2016	

Labeler - Allergan, Inc (144796497)

Establishment

Name	Address	ID/FEI	Business Operations
Forest Pharmaceuticals Inc		139645477	PACK(0023-5874)

Revised: 6/2016

Allergan, Inc