AMLOPRES-NB Tablets (Amlodipine + Nebivolol)

**Composition**

AMLOPRES-NB Tablets
Each uncoated tablet contains:
Amlodipine Besylate equivalent to Amlodipine .......... 5 mg
Nebivolol Hydrochloride equivalent to Nebivolol .......... 5 mg

**Dosage Form**

Tablet

**Description**

AMLOPRES-NB Tablets are a fixed-dose combination of amlodipine and nebulol.

**Pharmacology**

Amlodipine
Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro*, but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Hemodynamics
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically
significant changes in heart rate or blood pressures in normotensive patients with angina. With chronic once-daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; therefore, individuals with moderate hypertension (diastolic pressure: 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure: 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without a significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta-blockers to humans. Similar findings, however, have been observed in normals or well-compensated patients having heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects
Amlodipine does not change sinoatrial nodal function or atrioventricular (AV) conduction in intact animals or humans. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Nebivolol
Nebivolol is a beta-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses ≤10 mg, nebivolol is preferentially beta_{1} selective. In poor metabolizers and at higher doses, nebivolol inhibits both beta_{1}- and beta_{2}-adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane-stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, nebivolol does not demonstrate alpha_{1}-adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to beta-blocking activity. The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved include:
- Decreased heart rate
- Decreased myocardial contractility
- Diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers
- Suppression of renin activity
- Vasodilation and decreased peripheral vascular resistance

Pharmacokinetics
Amlodipine
After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6-12 hours. Absolute bioavailability has been estimated to be between 64-90%. The bioavailability of amlodipine is not altered by the presence of food.
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism, with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that, in hypertensive patients, approximately 93% of the circulating drug is bound to plasma proteins. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose.

Elderly patients and patients with hepatic impairment have decreased clearance of amlodipine with a resulting increase in area under the curve (AUC) of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

**Pediatric Patients**

Sixty-two hypertensive patients, aged 6-17 years, received doses of amlodipine between 1.25 mg and 20 mg. Resulting weight-adjusted clearance and volume of distribution were similar to values in adults.

Nebivolol

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to beta-blocking activity.

Plasma levels of d-nebivolol increase in proportion to dose in extensive metabolizers (EMs) and poor metabolizers (PMs) for doses up to 20 mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's beta receptor affinity is >1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher C_{max} and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

Absorption of nebivolol is similar to an oral solution. The absolute bioavailability has not been determined. Mean peak plasma nebivolol concentrations occur approximately 1.5-4 hours post-dosing in EMs and PMs. Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. Nebivolol may be administered without regard to meals.

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

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific 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.

**Special Populations**

**Renal Impairment**

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may, therefore, receive the usual initial dose.

Following a single 5 mg dose of nebivolol, the apparent clearance of nebivolol was unchanged in patients with mild renal impairment, reduced negligibly in patients with moderate impairment (CICr 30-50 mL/min, n=9), but reduced by 53% in patients with severe renal impairment (CICr <30 mL/min, n=5). The dose of nebivolol should, therefore, be adjusted in patients with severe renal impairment.

Nebivolol should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this
Hepatic Impairment

Patients with hepatic impairment have decreased clearance of amlodipine, with a resulting increase in the AUC of approximately 40-60%; hence, a lower initial dose may be required.

D-Nebivolol peak plasma concentrations 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). The starting dose should be reduced in patients with moderate hepatic impairment.

No formal studies have been performed in patients with severe hepatic impairment and nebivolol is contraindicated for these patients.

Pediatric Patients

Sixty-two hypertensive patients, aged 6-17 years, received doses of amlodipine between 1.25 mg and 20 mg. Resulting weight-adjusted clearance and volume of distribution were similar to values in adults.

Indications

For the treatment of essential hypertension in adults only.

Dosage And Administration

The recommended dosage is one tablet of AMLOPRES-NB once daily.

In elderly patients, the recommended starting dose is half tablet of AMLOPRES-NB once daily, which may be increased to one tablet once daily.

Renal Impairment

In patients with severe renal impairment (CICr <30 mL/min) the recommended initial dose is half tablet of AMLOPRES-NB; which may be increased to one tablet once daily. Since nebivolol has not been studied in patients receiving dialysis, AMLOPRES-NB is not recommended in these patients.

Hepatic Impairment

In patients with moderate hepatic impairment, the recommended initial dose is half tablet of AMLOPRES-NB; this may be increased to one tablet once daily. Since, nebivolol has not been studied in patients with severe hepatic impairment, AMLOPRES-NB is not recommended in severe hepatic impairment.

Contraindications

- Hypersensitivity to either component
- Severe bradycardia
- Heart block greater than first degree
- Cardiogenic shock
- Decompensated cardiac failure
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Hypertensives with severe hepatic impairment (Child-Pugh >B)

Warnings And Precautions
Drug Interactions

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin. Amlodipine has also been safely administered with digoxin, warfarin, phenytoin, indomethacin, cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, atorvastatin, sildenafil and ethanol.

Myocardial Depressants or Inhibitors of AV Conduction

AMLOPRES-NB should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists, or antiarrhythmic agents, such as disopyramide, are used concurrently. Both digitalis glycosides & beta-blockers slow atrioventricular conduction and decrease the heart rate. Concomitant use can increase the risk of bradycardia.

Catecholamine-Depleting Drugs

Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added beta-blocking action of nebivolol may produce excessive reduction of sympathetic activity.

Clonidine

In patients who are receiving AMLOPRES-NB and clonidine, AMLOPRES-NB should be discontinued for several days before the gradual tapering of clonidine.

CYP2D6 Inhibitors

Use caution when AMLOPRES-NB is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.)

Non-Dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents, and their electrocardiogram and blood pressure should be monitored.

Histamine-2 Receptor Antagonists

Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of d-nebivolol.

Sildenafil

The co-administration of nebivolol and sildenafil decreased the AUC and $C_{\text{max}}$ of sildenafil by 21% and 23% respectively. The effect on the $C_{\text{max}}$ and AUC for d-nebivolol was also small (<20%). The effect on vital signs (eg, pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Hypotensive Agents

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

Digitalis Glycosides

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease the heart rate. Concomitant use can increase the risk of bradycardia.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not
significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers
No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A4 inducers.

Cyclosporine
A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

Drug/Laboratory Test Interactions: None known.

- **Abrupt Cessation of Therapy**

Patients with coronary artery disease treated with AMLOPRES-NB should be advised against abrupt discontinuation of therapy with beta-blockers; severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported following such discontinuation. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. When discontinuation of AMLOPRES-NB is planned, patients should be carefully observed and advised to minimize physical activity. Nebivolol should be tapered over 1-2 weeks, when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that nebivolol be promptly reinstituted, at least temporarily.

- **Anesthesia and Major Surgery**

If AMLOPRES-NB is to be continued perioperatively, patients should be closely monitored when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If beta-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. The beta-blocking effects of nebivolol can be reversed by beta-agonists, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with beta-blockers.

- **Hypotension**

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely with amlodipine.

- **Increased Angina and/or Myocardial Infarction**

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy, or at the time of dosage increase. Nebivolol is not studied in patients with angina or who had a recent MI.

- **Bronchospastic Diseases**

In general, patients with bronchospastic diseases should not receive AMLOPRES-NB due to the beta-blocker component.

- **Heart Failure**

In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure, unless their condition has been stabilized.
Diabetes and Hypoglycemia

Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Non-selective beta-blockers may potentiate insulin-induced 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 AMLOPRES-NB should be used with caution.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Risk of Anaphylactic Reactions

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

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

Thyrotoxicosis

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

Pheochromocytoma

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

Renal Impairment

AMLOPRES-NB should be used with caution in hypertensives with severe renal impairment because of decreased renal clearance. Nebivolol has not been studied in patients receiving dialysis.

Hepatic Impairment

AMLOPRES-NB should be used with caution in hypertensives with moderate hepatic impairment because of decreased metabolism of amlodipine. Since nebivolol has not been studied in hypertensives with severe hepatic impairment is limited, nebivolol is contraindicated in these groups.

Pregnancy

Since there are no adequate studies on the use of amlodipine and nebivolol in pregnancy, AMLOPRES-NB should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Because of the potential for beta-blockers to produce serious adverse reactions, especially bradycardia, in nursing infants, AMLOPRES-NB is not recommended during nursing.

Pediatric Use

Safety and effectiveness of AMLOPRES-NB in pediatric patients has not been established. Pediatric studies in newborns and children up to 18 years of age have not been conducted for nebivolol because of the incomplete characterization of developmental toxicity and the possible adverse effects on long-term fertility.
Geriatric Use

Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Undesirable Effects

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine at doses up to 10 mg to placebo, discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema.

The incidence (%) of side effects that occurred in a dose related manner is as follows:

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>2.5 mg %</th>
<th>5 mg %</th>
<th>10 mg %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>1.8</td>
<td>3.0</td>
<td>10.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.1</td>
<td>3.4</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.7</td>
<td>1.4</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0.7</td>
<td>1.4</td>
<td>4.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Other adverse experiences that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Amlodipine (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7.3</td>
<td>7.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
</tr>
<tr>
<td>Edema</td>
<td>5.6</td>
<td>14.6</td>
</tr>
</tbody>
</table>
The following events occurred in 0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

- **Cardiovascular**: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.
- **Central and Peripheral Nervous System**: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
- **Gastrointestinal**: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
- **General**: allergic reaction, asthenia**, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
- **Musculoskeletal System**: arthralgia, arthrosis, muscle cramps**, myalgia.
- **Psychiatric**: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
- **Respiratory System**: dyspnea**, epistaxis.
- **Skin and Appendages**: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.
- **Special Senses**: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
- **Urinary System**: micturition frequency, micturition disorder, nocturia.
- **Autonomic Nervous System**: dry mouth, sweating increased.
- **Metabolic and Nutritional**: hyperglycemia, thirst.
- **Hemopoietic**: leukopenia, purpura, thrombocytopenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

**Nebivolol**

Clinical Studies Experience

Nebivolol has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

The data described below reflect worldwide clinical trial exposure to nebivolol in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received nebivolol for up to 24 months, with over 1900 patients treated for at least 6 months and approximately 1300 patients for more than one year.

In placebo-controlled clinical trials comparing nebivolol with placebo, discontinuation of therapy due to adverse reactions reported in 2.8% of patients treated with nebivolol and 2.2% of patients with placebo. The most common adverse reactions that led to discontinuation of nebivolol were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Table 1 lists treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg or 20-40 mg of nebivolol and

<table>
<thead>
<tr>
<th>Event</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20-40 mg</th>
<th>65 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>1.5</td>
<td>4.5</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1.4</td>
<td>3.3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.3</td>
<td>1.6</td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>
205 patients given placebo and for which the rate of occurrence of at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 1. Treatment-Emergent Adverse Reactions with an Incidence (over 6 weeks) > 1% in Nebivolol-Treated Patients at a Higher Frequency than Placebo-Treated Patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Placebo (n = 205) (%)</th>
<th>Nebivolol 5 mg (n = 459) (%)</th>
<th>Nebivolol 10 mg (n = 461) (%)</th>
<th>Nebivolol 20-40 mg (n = 677) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>Brasycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders</td>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Chest Pains</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>6</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Listed below are other reported adverse reactions with an incidence of at least 1% in more than 4300 patients treated with nebivolol in controlled or open-label trials except for those already appearing in Table 1, terms too general to be informative, minor symptoms or adverse reactions unlikely to be attributable to drug because they are common in the population. These adverse reactions were in most cases observed at a similar frequency in placebo-treated patients in
Body as a Whole: asthenia

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia

Nervous System Disorders: paraesthesia

Laboratory Abnormalities

In controlled monotherapy trials of hypertensive patients, nebivolol was associated with an increase in BUN, uric acid, triglycerides and decrease in HDL cholesterol and platelet count.

Post-marketing Experience

Amlodipine

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.

The following post-marketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Nebivolol

The following reactions have been identified from spontaneous reports of nebivolol received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to nebivolol. Adverse reactions common in the population have generally been omitted. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to nebivolol exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second- and third-degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritis, posriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo and vomiting.

Overdosage

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.
Nebivolol

The most common signs and symptoms associated with nebivolol overdosage are bradycardia and hypotension. Other important adverse events reported with nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with beta-blocker overdose include bronchospasm and heart block. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. If overdose occurs, nebivolol should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted:

- Bradycardia: Administer intravenous (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): Patients should be carefully monitored and treated 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, consideration should be given to the use of inotropic and vasodilating agents.
- Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled beta2-agonist and/or aminophylline.
- Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

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 nebivolol. Supportive measures should continue until clinical stability is achieved.

Packaging Information

Post-marketing Experience

AMLOPRES-NB: Strip pack of 10 tablets

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AMLOPRES-NB Tablets

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