Nebivolol

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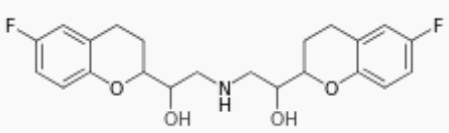

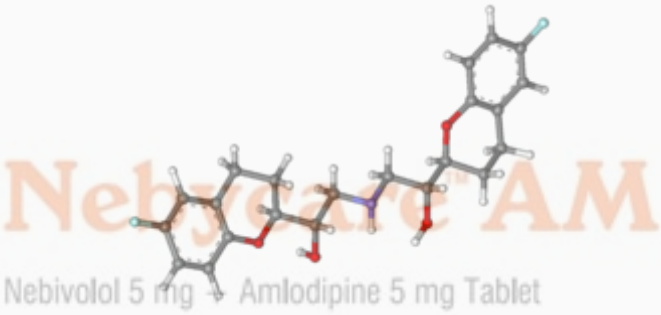

Systematic (IUPAC) name	
1-(6-Fluorochroman-2-yl)-{[2-(6-fluorochroman-2-yl)-2-hydroxy-ethyl]amino}ethanol OR 2,2'-Azanediylbis(1-(6-fluorochroman-2-yl)ethanol) OR 1-(6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-{[2-(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-hydroxyethyl]amino}ethan-1-ol	
Clinical data	
Trade names	Nebilet, Bystolic
AHFS/Drugs.com	monograph
MedlinePlus	a608029
Licence data	US FDA:link
Pregnancy cat.	C (US)
Legal status	POM (UK) ℞-only (US)

Routes	Oral
Pharmacokinetic data	
Protein binding	98%
Metabolism	Hepatic (CYP2D6-mediated)
Half-life	10 hours
Excretion	Renal and fecal
Identifiers	
CAS number	99200-09-6
ATC code	C07AB12
PubChem	CID 71301
DrugBank	DB04861
ChemSpider	64421
UNII	030Y90569U
KEGG	D05127
ChEMBL	CHEMBL434394
Chemical data	
Formula	$C_{22}H_{25}F_2NO_4$
Mol. mass	405.435 g/mol
SMILES	

- Fc4cc1c(OC(CC1)C(O)CNCC(O)C3Oc2ccc(F)cc2CC3)cc4

InChI

InChI=1S/C22H25F2NO4/c23-15-3-7-19-13(9-15)1-5-21(28-19)17(26)11-25-12-18(27)22-6-2-14-10-16(24)4-8-20(14)29-22/h3-4,7-10,17-18,21-22,25-27H,1-2,5-6,11-12H2

Key:KOHIRBRYDXPAMZ-UHFFFAOYSA-N

Nebivolol is a β_1 receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of hypertension and, in Europe, also for left ventricular failure.[1] It is highly cardioselective under certain circumstances.[1]

Pharmacology and biochemistry

β1 Selectivity

Beta blockers help patients with cardiovascular disease by blocking β receptors, while many of the side-effects of these medications are caused by their blockade of β2 receptors.[2] For this reason, beta blockers that selectively block β1 receptors (termed cardioselective or β1-selective beta blockers) produce fewer adverse effects (for instance, bronchoconstriction) than those drugs that non-selectively block both β1 and β2 receptors. Nebivolol has been marketed by Cipla Ltd under brand name Nebicip; by Forest Laboratories under the name Bystolic; by Micro Labs under the brand name Nebilong; ; and by Menarini under the names Hypoloc, Lobivon, Nebilet, Nebilox, Nobiten, and Temerit. In a laboratory experiment conducted on biopsied heart tissue, nebivolol proved to be the most β1-selective of the β-blockers tested, being approximately 3.5 times more β1-selective than bisoprolol.[3] However, the drug's receptor selectivity in humans is more complex and depends on the drug dose and the genetic profile of the patient taking the medication.[4] The drug is highly cardioselective at 5 mg.[5] However, at doses above 10 mg, nebivolol loses its cardioselectivity and blocks both β1 and β2 receptors.[4] (While the recommended starting dose of nebivolol is 5 mg, sufficient control of blood pressure may require doses up to 40 mg).[4] Furthermore, nebivolol is also not cardioselective when taken by patients with a genetic makeup that makes them “poor metabolizers” of nebivolol (and other drugs) or with CYP2D6 inhibitors.[4] As many as 1 in 10 whites and even more blacks are poor CYP2D6 metabolizers and therefore might benefit less from nebivolol's cardioselectivity although currently there are no directly comparable studies.

Vasodilator action

Nebivolol is unique as a beta-blocker.[6] Unlike carvedilol, it has a nitric oxide (NO)-potentiating, vasodilatory effect.[7][8] Along with labetalol, celiprolol and carvedilol, it is one of four beta blockers to cause dilation of blood vessels in addition to effects on the heart.[8] However, recent studies question the clinical relevance of this property to Nebivolol's efficacy.[9]

Antihypertensive effect

Nebivolol lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output.[10] The net hemodynamic effect of nebivolol is the result of a balance between the depressant effects of beta-blockade and an action that maintains cardiac output.[11] Antihypertensive responses were significantly higher with nebivolol than with placebo in trials enrolling patient groups considered representative of the U.S. hypertensive population, in Black patients, and in those receiving concurrent treatment with other antihypertensive drugs.[12]

Pharmacology of side-effect

Several studies have suggested that nebivolol has reduced typical beta-blocker-related side effects, such as fatigue, clinical depression, bradycardia, or impotence.[13][14][15] However, according to the FDA[16]

> Bystolic is associated with a number of serious risks. Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh > B) and in patients who are hypersensitive to any component of the product. Bystolic therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions. Finally, Bystolic is associated with other risks as described in the Adverse Reactions section of its PI. For example, a number of treatment-emergent adverse events with an incidence greater than or equal to 1 percent in Bystolic-treated patients and at a higher frequency than placebo-treated patients were identified in clinical studies, including headache, fatigue, and dizziness.

FDA warning letter about advertising claims

In late August 2008, the FDA issued a Warning Letter to Forest Laboratories citing exaggerated and misleading claims in their launch journal ad, in particular over claims of superiority and novelty of action.[16]

Contraindications

- Hepatic insufficiency
- Children
- Pregnancy
- Lactation

Adverse drug reactions

- Headache
- Parasthesia
- Dizziness

History

Mylan Laboratories licensed the U.S. and Canadian rights to nebivolol from Janssen Pharmaceutica N.V. in 2001. Nebivolol is already registered and successfully marketed in more than 50 countries, including the United States where it is marketed under the brand name Bystolic from Mylan Laboratories and Forest Laboratories. Nebivolol is manufactured by Forest Laboratories.

References

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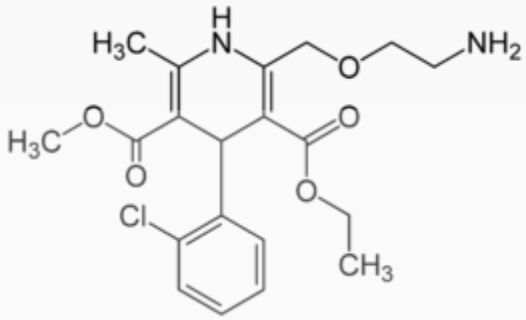
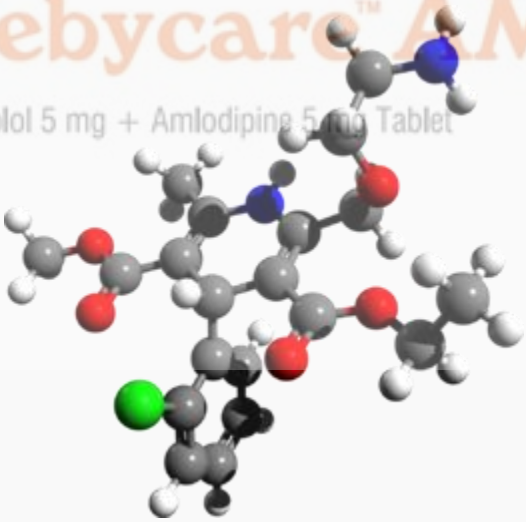
Nebycare™ AM

Nebivolol 5 mg + Amlodipine 5 mg Tablet

Amlodipine

Amlodipine





Systematic (IUPAC) name	
(*RS*)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate	
Clinical data	
AHFS/Drugs.com	monograph
MedlinePlus	a692044
Licence data	US FDA:link
Pregnancy cat.	C (AU) C (US)
Legal status	POM (UK) ℞-only (US)
Routes	Oral (tablets)
Pharmacokinetic data	
Bioavailability	64 to 90%
Metabolism	Hepatic

Half-life	30 to 50 hours
Excretion	Renal
Identifiers	
CAS number	88150-42-9
ATC code	C08CA01
PubChem	CID 2162
DrugBank	DB00381
ChemSpider	2077
UNII	1J444QC288
KEGG	D07450
ChEBI	CHEBI:2668
ChEMBL	CHEMBL1491
Chemical data	
Formula	$C_{20}H_{25}ClN_2O_5$
Mol. mass	408.879 g/mol
SMILES	• Clc1ccccc1C2C(=C(/N/C(=C2/C(=O)OCC)COCCN)C)\C(=O)OC
InChI	InChI=1S/C20H25ClN2O5/c1-4-28-20(25)18-15(11-27-10-9-22)23-12(2)16(19(24)26-3)17(18)13-7-5-6-8-14(13)21/h5-8,17,23H,4,9-11,22H2,1-3H3 Key:HTIQEAQVCYTUBX-UHFFFAOYSA-N

Amlodipine (as besylate, mesylate or maleate) is a long-acting dihydropyridine-type (DHP) calcium channel blocker used to lower blood pressure and to treat anginal chest pain. Amlodipine is regarded as the **Gold Standard** in terms of efficacy in reducing Hypertension. It offers 24 hours of BP control due to its long half life of 35-50 hours and is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.[1].

Like other calcium channel blockers, amlodipine lowers blood pressure by relaxing arterial smooth muscles, which decreases total peripheral resistance and therefore

reduces blood pressure. In angina, amlodipine increases blood flow to the heart muscle (although DHP-class calcium channel blockers are more selective for arteries than the muscular tissue of the heart (myocardium), as the calcium ion channels of the heart are not of the dihydropyridine-type).

Medical uses

Amlodipine is used in the management of hypertension[2] and coronary artery disease.[3]

Superior Benefits over other CCBs

- Amlodipine offers 24 hours smooth BP control due to its longest half-life of 35-50 hours among all CCBs.
- Amlodipine is well tolerated by the body
- Amlodipine reduces short term and long term BP variability and thereby effectively preventing cerobrovascular events.
- Amlodipine based regimen reduces relative risk of cardiovascular events.
- Amlodipine slows the progression of atherosclerosis in CAD patients.
- Amlodipine reduces transient myocardial ischemia in patients with coronary artery disease.
- Amlodipine increasees peripheral and coronary blood flow.

Clinical Trials on Amlodipine

Amlodipine is a proven USFDA backed, preferred molecule for controlling HT.

- Amlodipine is approved by US FDA & more widely available than other CCBs.
- Amlodipine is backed by 1331 clinical trials.
- A total of 4171 studies have been conducted on Amlodipine.

Contraindications

- Breast feeding
- Cardiogenic shock
- Unstable angina
- Systolic and diastolic blood pressure below 90/60 mmHg
- Aortic stenosis: Amlodipine causes vasodilation, which can result in reduced cardiac output in patients with severe aortic stenosis.

Adverse effects

Adverse side effects of the use of amlodipine may include:[4]

- Common: peripheral edema in 8.3% of users, fatigue in 4.5% of users[5] dizziness; palpitations; stomach-pain, headache, dyspepsia, somnolence(sleepiness) and/or nausea in greater than 1%.
- Uncommon: blood disorders, development of breasts in men (gynecomastia), impotence, depression, insomnia, tachycardia, or gingival enlargement - in one in 1,000 users
- Rarely: erratic behavior, hepatitis, jaundice - in one in 10,000 users
- Very rarely: hyperglycemia, tremor, Stevens–Johnson syndrome - in one in 100,000 users

The acute oral toxicity (LD50) of amlodipine in mice is 37 mg/kg.[6]

Cautions

- Hepatic impairment
- Pregnancy

Interactions

- In patients with severe coronary artery disease, amlodipine can increase the frequency and severity of angina or actually cause a heart attack on rare occasions.
- Excessive lowering of blood pressure during initiation of amlodipine treatment can occur, especially in patients already taking another medication for lowering blood pressure. In rare instances, congestive heart failure has been associated with amlodipine, usually in patients already on a beta blocker.
- Amlodipine is primarily metabolyzed by the liver, via the cytochrome P450 isoenzyme CYP3A4.[7] As a result, serum levels can potentially be affected by drugs which inhibit or activate CYP3A4. Grapefruit juice can inhibit the cytochrome P450 system,[7] but the predicted interaction risk with amlodipine is low.[8]

Mechanism of action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the movement of calcium ions into vascular smooth muscle cells and cardiac muscle cells. Experimental data suggest amlodipine binds to both dihydropyridine and nondihydropyridine 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, or decreased heart muscle contractility, 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 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.

Amlodipine also acts as a functional inhibitor of acid sphingomyelinase (FIASMA).[9] Sphingomyelin is involved in signal transduction and programmed cell death.

The precise mechanisms by which amlodipine relieves angina is not fully understood, but are thought to include:

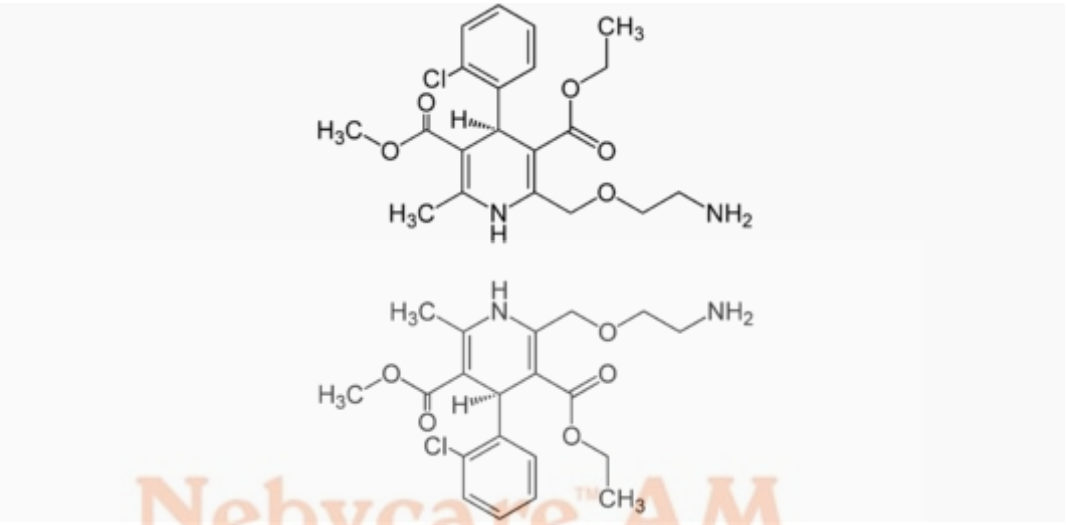
Stable angina
In patients with stable (exertional) angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, thereby lowering myocardial oxygen demand, at any given level of exercise.

Prinzmetal's angina
Amlodipine has been demonstrated to block spasm of the coronary arteries and restore blood flow in coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in Prinzmetal's angina.

Pharmacokinetics and metabolism

The metabolism and excretion of amlodipine have been studied in healthy volunteers following oral administration of ^{14}C-labelled drug.[10] Amlodipine is well absorbed by the oral route with a mean oral bioavailability of approximately 60%. Renal elimination is the major route of excretion with about 60% of an administered dose recovered in urine, largely as inactive pyridine metabolites. The major metabolite identified was 2-([4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl- 2-pyridyl]methoxy) acetic acid, and this represented 33% of urinary radioactivity. Amlodipine concentrations in plasma declined with a mean half-life of 33 h, while elimination of total drug-related material from plasma was slower.

Stereoisomerism



Amlodipine is a chiral calcium antagonist, currently on the market and in therapeutic use as a racemate [1:1 mixture of (*R*)-(+)- and (*S*)-(–)-amlodipine][11] A method for the semi-preparative chromatographic purification of the enantiomers (*S*)-(–)-amlodipine and (*R*)-(+)-amlodipine has been reported.[12]

Both enantiomers have different channel blocking activity.[13]

Preparations

Pfizer's patent protection on Norvasc lasted until 2007. Total patent expiration occurred later in 2007.[14] A number of generic versions are available.

In the United Kingdom, tablets of amlodipine from different suppliers may contain different salts. The strength of the tablets is expressed in terms of amlodipine base, i.e., without the salt. Tablets containing different salts are therefore considered interchangeable.

The efficacy and tolerability of a fixed-dose combination of amlodipine 5 mg and perindopril 4 mg, an angiotensin converting enzyme (ACE) inhibitor, have recently been confirmed in a prospective, observational, multicentre trial of 1250 hypertensive patients.[15]

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