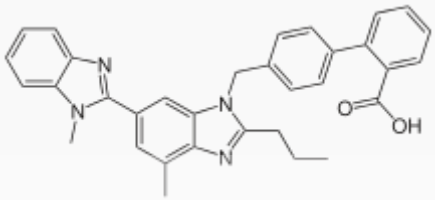
Telmisartan

Telmisartan



Systematic (IUPAC) name	
2-(4-{[4-Methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid	
Clinical data	
Trade names	Micardis
AHFS/Drugs.com	monograph
MedlinePlus	a601249
Pregnancy cat.	D (Au), D (U.S.)
Legal status	S4 (Au), POM (UK), ℞-only (U.S.)
Routes	Oral
Pharmacokinetic data	
Bioavailability	42–100%
Protein binding	≥99.5%
Metabolism	Minimal hepatic
Half-life	24 hours
Excretion	Faecal 97%
Identifiers	
CAS number	144701-48-4
ATC code	C09CA07
PubChem	CID 65999
IUPHAR ligand	592
DrugBank	DB00966
ChemSpider	59391
UNII	U5SYW473RQ

Bitalel AM
Telmisartan 40 mg Amlodipine 5 mg Tablet

KEGG	D00627
ChEBI	CHEBI:9434
ChEMBL	CHEMBL1017
Chemical data	
Formula	$C_{33}H_{30}N_4O_2$
Mol. mass	514.617 g/mol
SMILES	• O=C(O)c1ccccc1c2ccc(cc2)Cn3c4cc(cc(c4nc3CCC)C)c5nc6ccccc6n5C
InChI	InChI=1S/C33H30N4O2/c1-4-9-30-35-31-21(2)18-24(32-34-27-12-7-8-13-28(27)36(32)3)19-29(31)37(30)20-22-14-16-23(17-15-22)25-10-5-6-11-26(25)33(38)39/h5-8,10-19H,4,9,20H2,1-3H3,(H,38,39) Key:RMMXLENWKUUMAY-UHFFFAOYSA-N

Bitatel AM
Telmisartan 40 mg + Amlodipine 5 mg Tablet

Telmisartan (INN) /tɛlmɪˈsɑrtən/ is an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. It is marketed under the trade name **Micardis** (by Boehringer Ingelheim), among others.

Indication

Telmisartan is indicated in the treatment of essential hypertension.[1][2]

Administration

The usually effective dose telmisartan is 40–80 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily.[1]

Contraindications

Telmisartan is contraindicated during pregnancy. Like other drugs affecting the renin-angiotensin system (RAS), telmisartan can cause birth defects, stillbirths, and neonatal deaths. It is not

known whether the drug passes into the breast milk.[3] Also it is contraindicated in bilateral renal artery stenosis in which it can cause renal failure.

Side effects

Side effects are similar to other angiotensin II receptor antagonists and include tachycardia and bradycardia (fast or slow heartbeat), hypotension (low blood pressure), edema (swelling of arms, legs, lips, tongue, or throat, the latter leading to breathing problems), and allergic reactions.[3]

Mode of action

Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT_1), with a binding affinity 3000 times greater for AT_1 than AT_2. It has the longest half-life of any ARB (24 hours)[1][4] and the largest volume of distribution among ARBs (500 liters).[5][6]

In addition to blocking the RAs, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).[4]

Telmisartan's activity at the PPAR-γ receptor has prompted speculation around its potential as a sport doping agent as an alternative to GW 501516.[7] Telmisartan activates PPARδ receptors in several tissues.[8][9][10][11]

Clinical trials

ONTARGET

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) was one of the largest ARB clinical studies ever undertaken;[12] 25,620 patients from 733 centres in 41 countries were randomised for 5.5 years of treatment of either telmisartan, the ACE inhibitor ramipril or a combination of the two. The study aimed to investigate the role of telmisartan in cardiovascular (CV) protection through the primary composite outcome of death from CV causes, myocardial infarction, stroke or hospilization for heart failure, in high CV risk patients.

The study showed telmisartan was as effective as ramipril but with lower rates of cough and angioedema, which led to fewer discontinuations. The combination group experienced similar efficacy, but with increased risk of hypotensivesymptoms. Moreover, in a patient population selected to tolerate ACE inhibitors, telmisartan was shown to be better tolerated and associated with higher treatment compliance than ramipril.[13]

TRANSCEND

As part of the ONTARGET study, patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo as part of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) study. An accompanying editorial comments: "Overall, data supporting use of angiotensin-receptor blockers to prevent vascular events in various cardiovascular groups, other than heart failure, are incomplete. TRANSCEND's results challenge the non-inferiority shown in ONTARGET and suggest no more than a modest effect, if any at all."[14]

PRoFESS

The Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) study investigated therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years. This treatment did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.[15]

See also

- Discovery and development of angiotensin receptor blockers
- GW 501516

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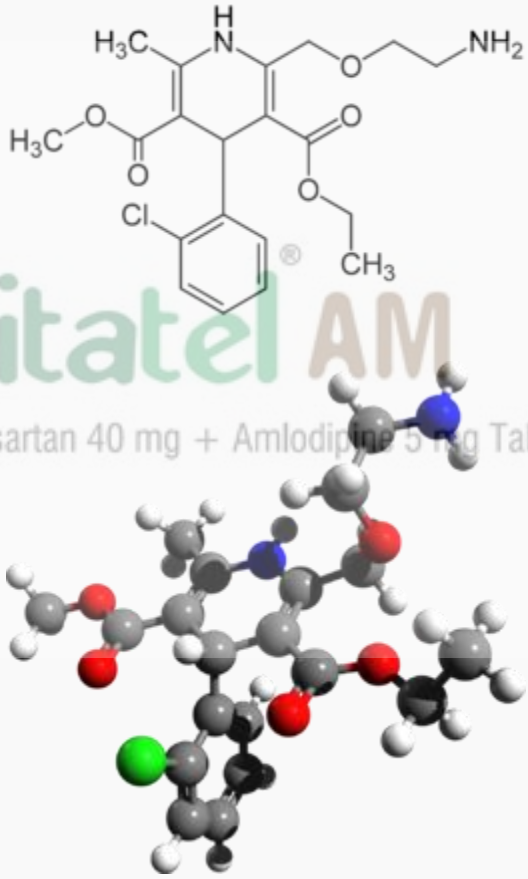
Bitatel AM
Telmisartan 40 mg + Amlodipine 5 mg Tablet

Amlodipine

Amlodipine



Bitatel AM
Telmisartan 40 mg + Amlodipine 5 mg Tablet

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

BitatelAM
Telmisartan 40 mg + Amlodipine 5 mg Tablet

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 cerebrovascular 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.

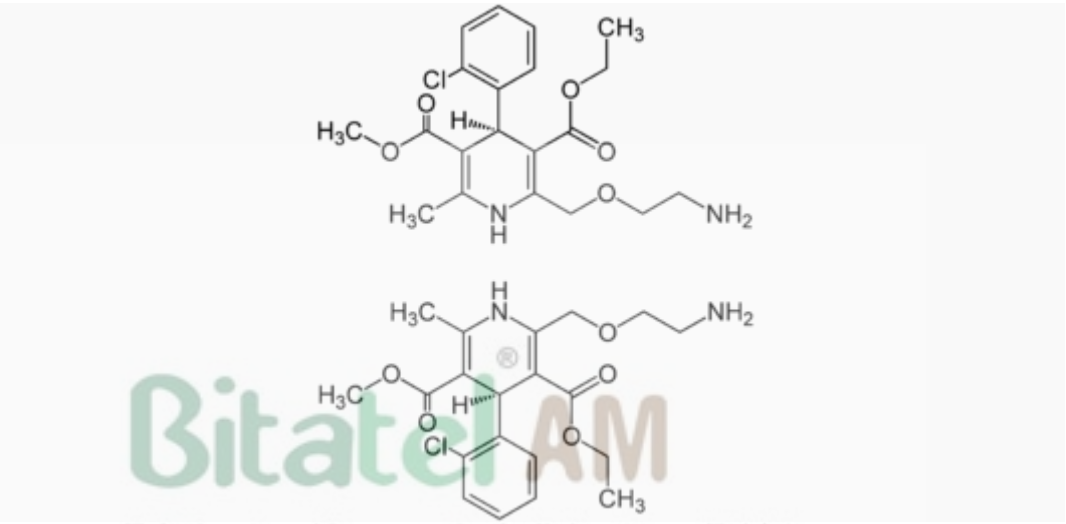
Prinzmetal's angina
Amlodipine has been demonstrated to block spasm of the coronary arteries and restore blood flow in coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels *in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



Telmisartan 40 mg + Amlodipine 5 mg Tablet

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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