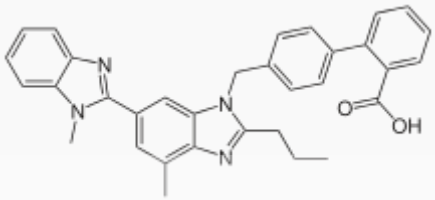
Telmisartan

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 CH
Telmisartan 40 mg + Chlorthalidone 12.5 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 CH
Telmisartan 40 mg+ Chlorthalidone 12.5 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 40 mg + Chlorthalidone 12.5 mg Tablet

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

References

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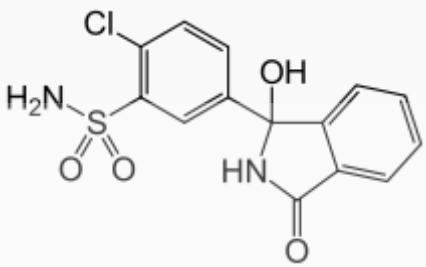
Telmisartan 40 mg+ Chlorthalidone 12.5 mg Tablet

Chlorthalidone

Chlortalidone



Bitatel
Telmisartan 40 mg + Chlorthalidone 12.5 mg Tablet

Systematic (IUPAC) name

(*RS*)-2-Chloro-5-(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)benzene-1-sulfonamide

Clinical data	
Trade names	Hygroton, Tenoretic
AHFS/Drugs.com	Consumer Drug Information
MedlinePlus	a682342
Pregnancy cat.	C (Au), B (U.S.)
Legal status	POM (UK)
Routes	Oral
Pharmacokinetic data	

Protein binding	75%
Half-life	40 hours
Excretion	Renal
Identifiers	
CAS number	77-36-1
ATC code	C03BA04
PubChem	CID 2732
DrugBank	DB00310
ChemSpider	2631
UNII	Q0MQD1073Q
KEGG	D00272
ChEBI	CHEBI:3654
ChEMBL	CHEMBL1055
Chemical data	
Formula	$C_{14}H_{11}ClN_2O_4S$
Mol. mass	338.766 g/mol

Bitatel CH
Telmisartan 40 mg + Chlorthalidone 12.5 mg Tablet

SMILES

- O=S(=O)(N)c1c(Cl)ccc(c1)C2(O)c3ccccc3C(=O)N2

InChI

- InChI=1S/C14H11ClN2O4S/c15-11-6-5-8(7-12(11)22(16,20)21)14(19)10-4-2-1-3-9(10)13(18)17-14/h1-7,19H,(H,17,18)(H2,16,20,21)

Key:JIVPVXMEBJLZRO-UHFFFAOYSA-N

Chlortalidone (INN/BAN) or **chlorthalidone** (USAN) is a diuretic drug used to treat hypertension, originally marketed as Hygroton in the USA. It is described as a thiazide diuretic (or, rather, a thiazide-like diuretic because it acts similarly to the thiazides but does not contain the benzothiadiazine molecular structure). Compared with other medications of the thiazide class, chlortalidone has the longest duration of action but a similar diuretic effect at maximal therapeutic doses. It is often used in the management of hypertension and edema. Unlike loop diuretics, chlortalidone efficacy is diminished in patients with certain renal diseases (e.g. chronic renal disease). A clinical trial (ALLHAT) in 2002 compared chlortalidone to doxazosin in the treatment of high-risk hypertensive patients. In this study, only chlortalidone significantly reduced the risk of combined cardiovascular disease events, especially heart failure, when compared with drugs such as doxazosin.[1] Chlortalidone was approved by the FDA in 1960. The ALLHAT study conclusions showed that there was no significant difference in all-cause mortality, fatal heart disease, or non-fatal myocardial infarction when chlortalidone was compared with lisinopril or amlodipine but did show decrease rates of heart failure after 6 years when compared with amlodipine and decreased rates of cerebrovascular disease after 6 years when compared with lisinopril leading the study conclusions to say that thiazide-type diuretics are preferred first-step in antihypertensive therapy.
In terms of activity, chlorothalidone is very similar to hydrochlorothiazide benzothiadiazide and is used as an independent drug or in combination with other antihypertensive agents for lowering arterial blood pressure, and also as an adjuvant drug for treating edema caused by cardiac insufficiency and renal irregularities, including nephrotic syndrome.

Eritel CH
Telmisartan 40 mg + Chlorthalidone 12.5 mg Tablet

Mechanism of action

Chlortalidone prevents reabsorption of sodium and chloride by inhibiting the Na^+/Cl^- symporter in the distal convoluted tubule. Thiazides and related compounds also decrease the glomerular filtration rate, which further reduces the drug's efficacy in patients with renal impairment (e.g. renal insufficiency). By increasing the delivery of sodium to the distal renal tubule, chlortalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism (i.e. apical ROMK/Na channels coupled with basolateral NKATPases). This can result in hypokalemiaand hypochloremia as well as a mild metabolic alkalosis; however, the diuretic efficacy of chlortalidone is not affected by the acid-base balance of the patient being treated. Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Eventually, cardiac output returns to normal, and plasma and extracellular fluid volume return to slightly less than normal, but a reduction in peripheral vascular resistance is maintained, thus resulting in an overall lower blood pressure. The reduction in intravascular volume induces an elevation in plasma renin activity and aldosterone secretion, further contributing to the potassium loss associated with thiazide diuretic therapy.

Combination products

It is also available as a combination product with the beta blocker atenolol, marketed in the UK as co-tenidone and in the US as Tenoretic.

Recently, products containing chlortalidone in combination with angiotensin receptor blockers telmisartan (Eritel CH in India), olmesartan (Olmin CH[2] in India) and AzilsartanEdarbyclorhave been marketed .

Synthesis

1st method

Chlorothalidone can be synthesized by two proposed methods from 2'-carboxy-4-chlorobenzophenone, which is easily synthesized by acylating chlorobenzol with phthalic anhydride in the presence of aluminium chloride. The resulting benzophenone derivative undergoes nitration by nitric acid, which gives 2'-carboxy-3-nitro-4-chlorobenzophenone. The nitro group in the resulting compound is reduced by tin dichloride to 2'-carboxy-3-amino-4-

chlorobenzophenone. Next, subsequent diazotization and reaction with sulfur dioxide in the presence of copper dichloride gives the corresponding sulfonylchloride. Upon reaction with thionyl chloride, this compound undergoes cyclization into a phthalide, which when reacted with aqueous ammonia rearranges into a derivative of isoindoline with simultaneous substitution of the chloride atom in the sulfogroup with an amino group, which results in chlorothalidone.

2nd method

A second way of synthesizing it is from 2'-carboxy-4-chlorobenzophenone, which during reduction with zinc in acetic acid transforms into 3-(4'-chlorophenyl)phthalide. Sulfonylchlorination of this gives the corresponding sulfonyl chloride, which upon reaction with phosphorus pentachloride is chlorinated into 3-(4'-chlorophenyl-3'-chlorosulfo)-3-chlorophtalide. This is reacted with aqueous ammonia in the aforementioned manner, and it rearranges into chlorothalidone.

3rd method

A third way of synthesis is started from 2'-carboxy-4-chlorobenzophenone, and it consists of direct cyclization of the indicated carboxy benzophenone into 3-(4-chlorophenyl)phthalimidine. Subsequent sulfochlorination and amination of this product gives 2-chloro-5-(3-oxo-1-isoindolinyl)-benzolsulfonamide, which is oxidized by various oxidizers such as oxygen or hydrogen peroxide in alkaline or chromic acid in acetic acid into chlorothalidone.

Citatel.cz

In terms of activity, chlorothalidone is very similar to benzothiadiazide and is used as an independent drug or in combination with other antihypertensive agents for lowering arterial blood pressure, and also as an adjuvant drug for treating edema caused by cardiac insufficiency and renal irregularities, including nephrotic syndrome.

Formulation: 10 mg Chlorthalidone 125 mg Tablet

Synonyms of this drug are gigroton, novatalidon, uridon and others.

References

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