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ALISKIREN: ONE NAME MANY ACTION

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Abstract: Aliskiren (brand names Tekturna and Rasilez) is the first in a class of drugs called direct renin inhibitors. It is used for essential (primary) hypertension. While used for high blood pressure, other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit. In December 2011, Novartis halted a trial of the drug after discovering increased nonfatal stroke, kidney complications, high blood potassium, and low blood pressure in people with diabetes and kidney problems.

As a result, in 2012: A new contraindication was added to the product label concerning the use of aliskiren with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) in patients with diabetes because of the risk of kidney impairment, low blood pressure, and high levels of potassium in the blood. A warning to avoid use of aliskiren with ARBs or ACEIs was also added for patients with moderate to severe kidney impairment (i.e., where glomerular filtration rate is less than 60 ml/min). Novartis decided to stop marketing Valturna (aliskiren/valsartan). Aliskiren was co-developed by the Swiss pharmaceutical companies Novartis and Speedel.

Keywords: Hypertension, Renin Inhibitor

Aliskiren:

- Brand Name: Tekturna and Rasilez
- Type: Small Molecule
- Weight: 551.758 $g.mol^{-1}$
- Chemical Formula: $C_{30}H_{53}N_3O_6$
- Associated Conditions: High Blood Pressure
- Aliskiren is a Renin Inhibitor
- Absorbance: GI Tract (Poorly Absorb)
- Bioavailability: 2.0 & 2.5%
- Peak Plasma Concentration: 1-3 hours after administration.
- Steady Plasma Concentration: 7-8 Days of regular Administration
- Route of Administration: By Mouth (Tablet)

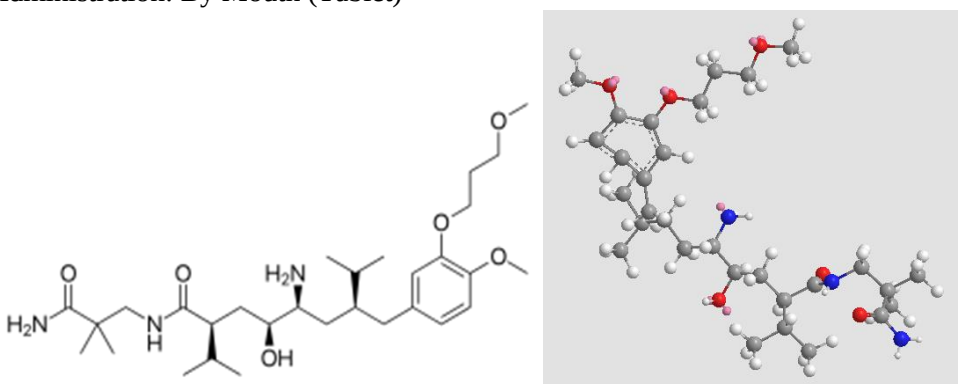


Figure-1: Chemical Structure

Aliskiren (formerly CGP 60536) was discovered in Ciba-Geigy (now Novartis, Basel, Switzerland) through a combination of molecular modelling and crystallographic structure analysis.

Introduction: Aliskiren [CAS Number: 173334-57-1; (2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-8-methyl-2-(propan-2-yl)nonanamide] is the first drug in the renin inhibitor drug class and is used for the treatment of hypertension. It was developed by Speedel and Novartis and initially approved by the FDA in early 2007. Aliskiren has been proven to efficacious in reducing blood pressure when used alone or in conjunction with other antihypertensive agents.[1]

Pharmacodynamics: Aliskiren reduces blood pressure by inhibiting renin. This leads to a cascade of events that decreases blood pressure, lowering the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarction.[2]

Aliskiren Synthesis:

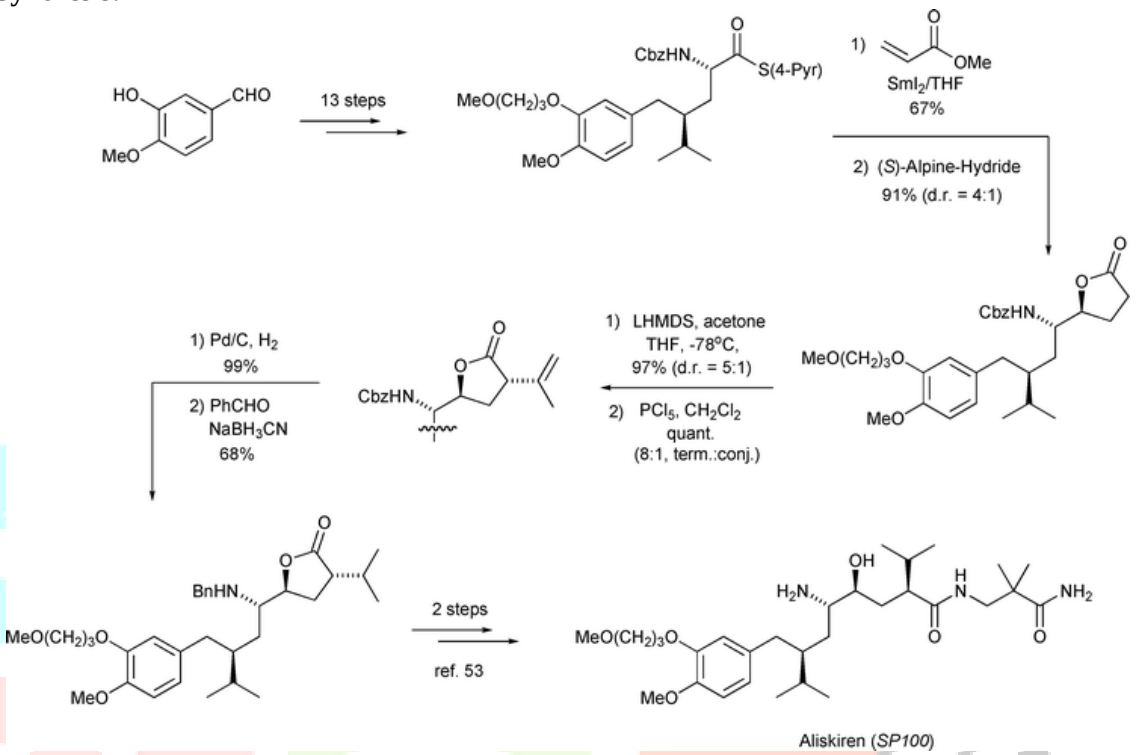


Figure-2: Synthesis of Aliskiren

Absorption: Aliskiren is absorbed in the gastrointestinal tract and is poorly absorbed with a bioavailability between 2.0 and 2.5%. Peak plasma concentrations of aliskiren are achieved between 1 to 3 hours after administration. Steady-state concentrations of aliskiren are achieved within 7-8 days of regular administration.[3]

Mechanism of action: Aliskiren is a renin inhibitor. Renin is secreted by the kidneys when blood volume and renal perfusion decrease. It normally cleaves the protein angiotensinogen to form angiotensin I. Angiotensin I is then converted to angiotensin II, an active protein. Angiotensin II is a potent vasoconstrictor that causes the release of catecholamines into the circulation. It also promotes the secretion of aldosterone in addition to sodium reabsorption, increasing blood pressure. Additionally, angiotensin II acts on the adrenal cortex where it stimulates aldosterone release. Aldosterone increases sodium reabsorption and potassium excretion in the nephron.[4]

Aliskiren prevents the above process via binding to renin at its active site, stopping the cleavage of angiotensin, in turn inhibiting the formation of angiotensin I. This ends the cascade of angiotensin II mediated mechanisms that normally increase blood pressure.[5]

Figure-3: Aliskiren formulation

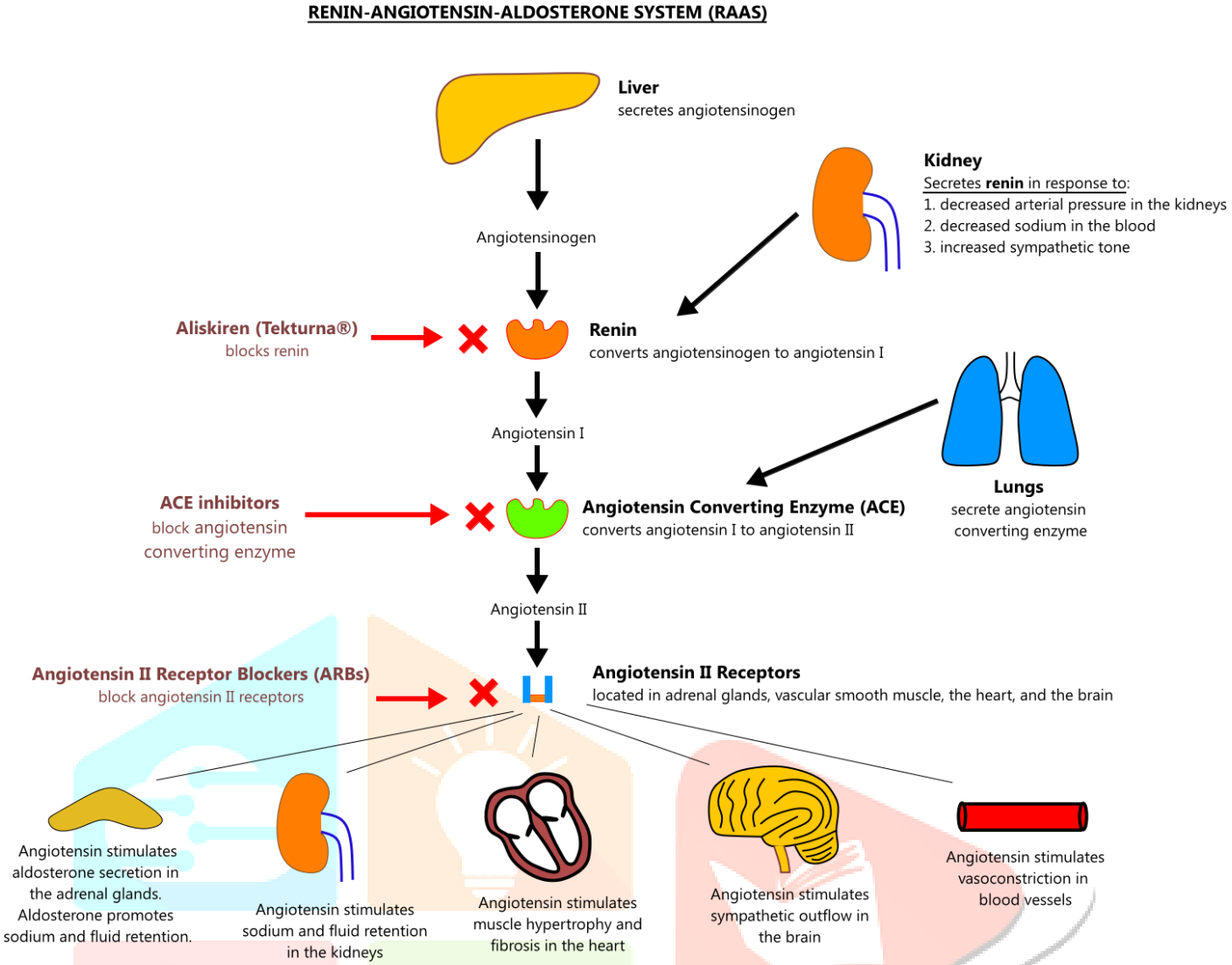


Figure-4: Aliskiren Mechanism Of Action

Absorption: Aliskiren is absorbed in the gastrointestinal tract and is poorly absorbed with a bioavailability between 2.0 and 2.5%. Peak plasma concentrations of aliskiren are achieved between 1 to 3 hours after administration. Steady-state concentrations of aliskiren are achieved within 7-8 days of regular administration.[6]

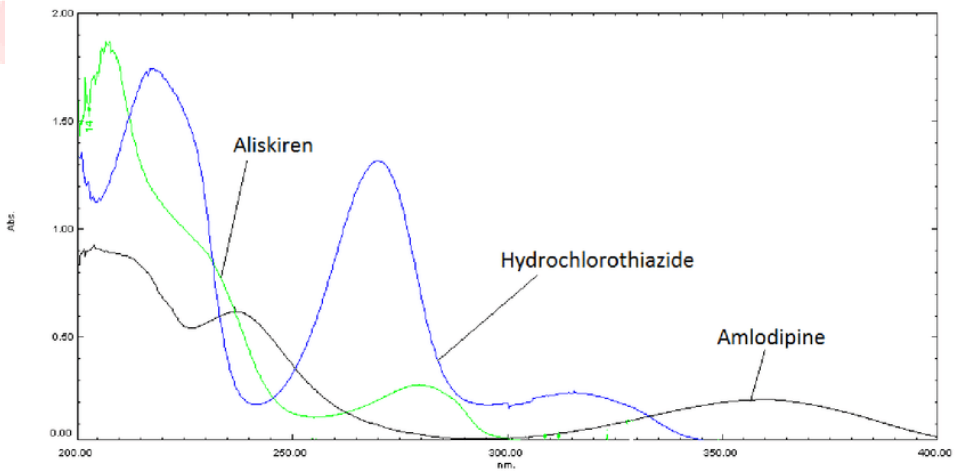


Figure-5: Aliskiren metabolism

Aliskiren, an orally active non-peptide renin inhibitor, was the first drug in its class on the market. It is used to treat hypertension as monotherapy or in combination with other antihypertensive agents. The key to the discovery of aliskiren was crystallography and molecular modeling techniques. Now, a solution has been found to the problem that impeded the development of the renin inhibitors of the previous generations. Non-peptide substances were known to be able to solve the problems of poor pharmacokinetic properties and low specificity. This led to the design of small molecules, non-peptide inhibitors, which were very potent and specific of human renin. However, caused by their chemical structure even third-generation renin inhibitors are difficult to resorb by the human body and their oral bioavailability is often below 2%.

The renin molecule is a monospecific enzyme that belongs to the aspartic protease family. Its structure is complex and consists of two homologous lobes that fold mainly in a β-sheet conformation. Between the two lobes, deep within the enzyme, resides the active site, and its catalytic activity is due to two aspartic acid residues (Asp32 and Asp 215, one from each lobe in the renin molecule). A flexible flap made from amino acids formed in a β-hairpin closes the active site by covering the cleft. The renin molecule contains both hydrophobic and hydrophilic amino acids. The hydrophilic ones tend to be on the outside of the molecule, while the hydrophobic ones tend to be more on the inside and form the active site, a large hydrophobic cavity that can accommodate a ligand with at least seven residues. The principal connection between a ligand and the enzyme is by hydrogen bonding. The residues are named after their places in the ligand, the residues closest to the cleavage site are named P1 and P1′ and they bind into the S1 and S1′ pockets, respectively. There are four S pockets, and three S′ pockets (Table-1). The pockets alternate on either side of the backbone in the ligand. This alternation affects the orientation of the pockets, making the S3 and S1 pockets arrange together and the S2 pocket close to both S4 and S1′ pockets. Evidence suggests the closely arranged S1 and S3 pockets merge to form a spacious superpocket. Ligands that fill the superpocket have greater potency than those which do not, occupying increases potency 200-fold. These ligands can be structurally diverse and form van der Waals bonds to the surface of the superpocket. From the S3 pocket stretches a binding site distinct for renin, the S3sp subpocket. The S3sp subpocket can accommodate both hydrophobic and polar residues, the pocket can accommodate three water molecules, but has also lipophilic nature. The S3sp subpocket is not conformationally flexible, so the residues occupying the pocket must have certain characteristics. They cannot be sterically demanding and must have reasonably high number of rotatable bonds and be able to connect with hydrogen bonds. The S2 pocket is large, bipartite and hydrophobic, but can accommodate both hydrophobic and polar ligands. This diversity of possible polarity offers the P2 residue opportunity of variation in its connection to the enzyme. The S3-S1 and the S3sp subpockets have been the main target of drug design, but recent discoveries have indicated other sites of interest. Interactions to the pockets on the S′ site have been proven to be critical for affinity, especially the S1′ and S2′, and in vitro tests have indicated the interaction with the flap region could be important to affinity.[7]

Interaction with both aspartic acids in the active site results in a higher affinity. Higher affinity also results by occupying more active site pockets. However, some pockets contribute more to the affinity than others. A hydrophobic interaction with the S3sp subpocket, S1 and S3 contribute to higher potency and affinity. By having a large and aromatic residue in P3 increases inhibitory activity. Occupation of the S3sp subpocket can increase potency by 50-fold and results in tight binding. Example of binding to the renin inhibitor: Aliskiren is a peptide-like renin inhibitor and, unlike most, it is rather hydrophilic. It blocks the catalytic function of the enzyme by occupying the S3 to S2′ pockets, except the S2 pocket. Aliskiren also binds to the S3sp subpocket and because that pocket is distinct for renin, aliskiren does not inhibit other aspartic proteases, such as cathepsin D and pepsin. The side chain of aliskiren binds the S3sp subpocket ideally, and leads to its quality as an inhibitor of human renin. The hydroxyl group in aliskiren forms a hydrogen bond with both oxygen atoms of the Asp32. The amine group forms a hydrogen bond with the carboxylic acid group of Gly217 and the oxygen atom of the Asp32.

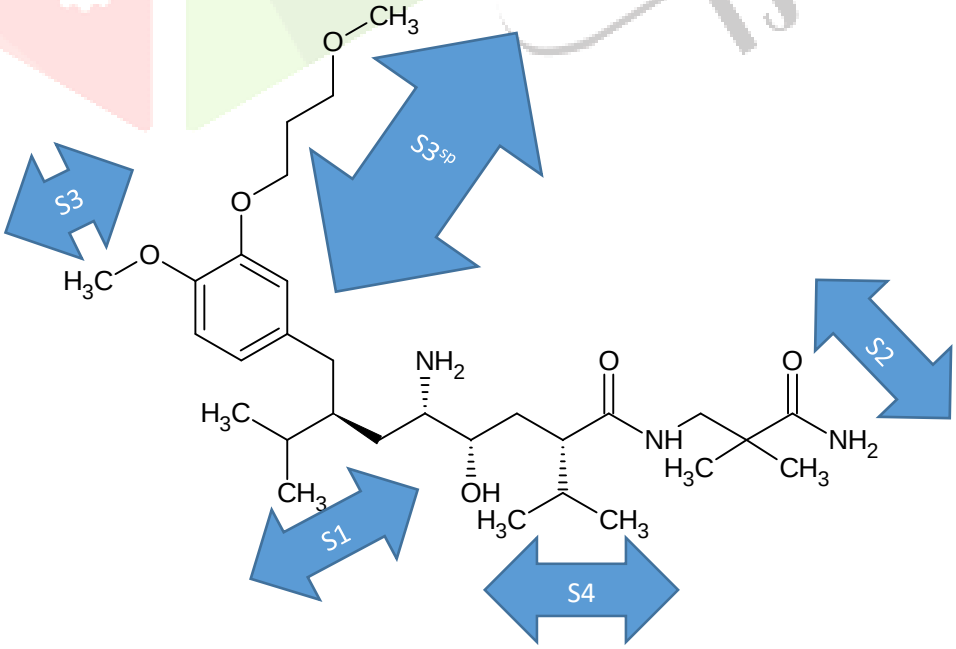


Figure-6: Aliskiren binding pocket in receptor

The methoxy group on the aromatic ring fills the S3 pocket and may possibly form a hydrogen bond with a secondary amine group of Tyr14. The amide group forms a hydrogen bond with a secondary amine group of Ser76. The S1 and S1′ pockets are occupied by the two propyl groups in positions P1 and P1′. The terminal amide in position P2′ anchors the amide tail in the active site by forming a hydrogen bond with Arg74 in the S2′ pocket.[8]

Pocket	Characteristics	Sub site	Importance to binding
S4	Hydrophobic	P4	Relatively important for binding
S3	Hydrophobic	P3	Very important for binding
$S3^{sp}$	Equally hydrophobic/-philic	P3 side chain	Dramatically enhances binding affinity
S2	Large and hydrophobic	P2	Important for binding
S1	Large and hydrophobic	P1	NA
S1′	Primarily hydrophobic	P1′	Critical for tight binding
S2′	Polar	P2′	Critical for tight binding
S3′	NA	P3′	Structure and presence is not as important

Table-1: Absorption of Aliskiren

Metabolism: About 80% of the drug in plasma following oral administration is unchanged. Two major metabolites account for about 1-3% of aliskiren in the plasma. One metabolite is an O-demethylated alcohol derivative and the other is a carboxylic acid derivative. Minor oxidized and hydrolyzed metabolites may also be found in the plasma.

Route of elimination: Aliskiren is mainly excreted via the hepatobiliary route and by oxidative metabolism by hepatic cytochrome enzymes. Approximately one-quarter of the absorbed dose appears in the urine as unchanged parent drug. One pharmacokinetic study of radiolabeled aliskiren detected 0.6% radioactivity in the urine and more than 80% in the feces, suggesting that aliskiren is mainly eliminated by the fecal route.[9]

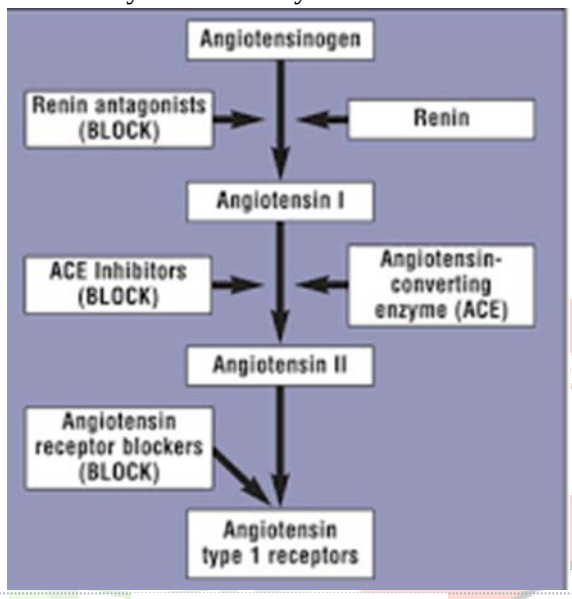


Figure-7: ACE inhibition

Clearance: Aliskiren is partially cleared in the kidneys, and safety data have not been established for patients with a creatinine clearance of less than 30 mL/min. One pharmacokinetic study revealed an average renal clearance of 1280 +/- 500 mL/hour in healthy volunteers.

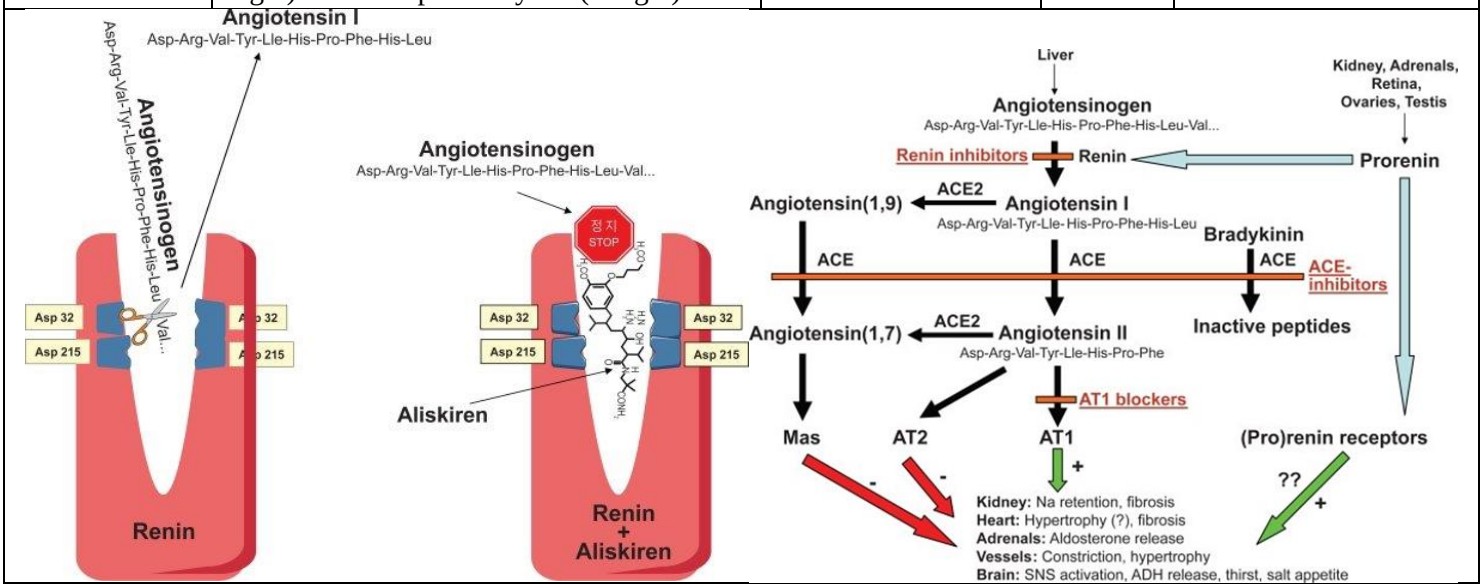
Toxicity: The oral LD50 of aliskiren in rats is >2000 mg/kg. Overdose information is limited in the literature, however, an overdose with aliskiren is likely to result in hypotension. Supportive treatment should be initiated in the case of an overdose. Interaction with both aspartic acids in the active site results in a higher affinity. Higher affinity also results by occupying more active site pockets.[10]

Drug Interactions

DRUG	INTERACTION
Abametapir	The serum concentration of Aliskiren can be increased when it is combined with Abametapir.
Acebutolol	Acebutolol may increase the hypotensive activities of Aliskiren.
Aceclofenac	The risk or severity of renal failure and hypertension can be increased when Aceclofenac is combined with Aliskiren.
Acemetacin	The risk or severity of renal failure and hypertension can be increased when Acemetacin is combined with Aliskiren.
Acetylsalicylic acid	The risk or severity of renal failure and hypertension can be increased when Acetylsalicylic acid is combined with Aliskiren.
Alclofenac	The risk or severity of renal failure and hypertension can be increased when Alclofenac is combined with Aliskiren.
Aldesleukin	The risk or severity of adverse effects can be increased when Aldesleukin is combined with Aliskiren.
Alfentanil	Alfentanil may decrease the antihypertensive activities of Aliskiren.
Alfuzosin	Alfuzosin may increase the hypotensive activities of Aliskiren.
Almotriptan	Almotriptan may decrease the antihypertensive activities of Aliskiren.

Mixture Products

NAME	INGREDIENTS	DOSAGE	ROUTE	LABELLER
Amturnide	Aliskiren hemifumarate (300 mg/1) + Amlodipine besylate (5 mg/1) + Hydrochlorothiazide (25 mg/1)	Tablet, film coated	Oral	Novartis
Amturnide	Aliskiren hemifumarate (300 mg/1) + Amlodipine besylate (10 mg/1) + Hydrochlorothiazide (25 mg/1)	Tablet, film coated	Oral	Novartis
Amturnide	Aliskiren hemifumarate (300 mg/1) + Amlodipine besylate (5 mg/1) + Hydrochlorothiazide (12.5 mg/1)	Tablet, film coated	Oral	Novartis
Amturnide	Aliskiren hemifumarate (300 mg/1) + Amlodipine besylate (10 mg/1) + Hydrochlorothiazide (12.5 mg/1)	Tablet, film coated	Oral	Novartis
Amturnide	Aliskiren hemifumarate (150 mg/1) + Amlodipine besylate (5 mg/1) + Hydrochlorothiazide (12.5 mg/1)	Tablet, film coated	Oral	Novartis
Rasilez HCT	Aliskiren hemifumarate (150 mg) + Hydrochlorothiazide (25 mg)	Tablet	Oral	Noden Pharma Dac
Rasilez HCT	Aliskiren hemifumarate (300 mg) + Hydrochlorothiazide (25 mg)	Tablet	Oral	Noden Pharma Dac
Rasilez HCT	Aliskiren hemifumarate (150 mg) + Hydrochlorothiazide (12.5 mg)	Tablet	Oral	Noden Pharma Dac
Rasilez HCT	Aliskiren hemifumarate (300 mg) + Hydrochlorothiazide (12.5 mg)	Tablet	Oral	Noden Pharma Dac
Tekamlo	Aliskiren hemifumarate (300 mg/1) + Amlodipine besylate (5 mg/1)	Tablet, film coated	Oral	Novartis



Conclusion: Pregnancy: Other drugs such as ACE inhibitors, also acting on the renin–angiotensin system, have been associated with fetal malformations and neonatal death. Angiotensin cannot be used in patients who are pregnant because it will result in disruption of normal fatal kidney development.
Breastfeeding: During animal studies, the drug has been found present in milk.
Aliskiren has been shown to increase the likelihood of adverse cardiovascular outcomes in patients with diabetes and kidney or heart disease. It reduces furosemide blood concentration.
Atorvastatin may increase blood concentration, but no dose adjustment is needed.
Due to possible interaction with ciclosporin, the use of ciclosporin and aliskiren at the same time is contraindicated.
Caution should be exercised when aliskiren is administered with ketoconazole or other moderate P-glycoprotein inhibitors (itraconazole, clarithromycin, telithromycin, erythromycin, or amiodarone).
Recommendations have been made to stop prescribing aliskiren-containing medicines to patients with diabetes (type 1 or type 2) or with moderate to severe kidney impairment who are also taking an ACE inhibitor or ARB. Such patients should consider alternative antihypertensive treatment as necessary.
Many drugs control blood pressure by interfering with angiotensin or aldosterone. However, when these drugs are used chronically, the body increases renin production, which drives blood pressure up again. Therefore, pharmacologists have been looking for a drug to inhibit renin directly. Aliskiren is the first drug to do so.

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