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# TELAVANCIN: A LIPOGLYCOPEPTIDE FOR THE TREATMENT OF COMPLICATED SKIN & SKIN STRUCTURE INFECTIONS

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Currently, vancomycin is the mainstay of therapy for treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Recent epidemiologic data have highlighted the decreasing susceptibility of MRSA to vancomycin[2,3] and the development of vancomycin resistant enterococcus (VRE) strains, requiring the development of newer antibiotics. Theravance Inc, on September 11th 2009, received FDA approval for Telavancin (Vibativ®), a novel lipoglycopeptide, which targets gram-positive organisms including MRSA, heteroresistant vancomycin intermediate *Staphylococcus aureus* (hVISA), vancomycin-intermediate *Staphylococcus aureus* (VISA), and vancomycin-resistant *Staphylococcus aureus* (VRSA). This article will describe the pharmacokinetics and pharmacodynamics of telavancin, the FDA approved indication for complicated skin and skin structure infections (cSSSI), pending approval for pneumonia, and a safety analysis. Lastly, a cost comparison of vancomycin to telavancin will be provided.

## PHARMACOLOGY

*Mechanism of Action*

Similar to vancomycin, telavancin inhibits cell wall synthesis by binding to peptidoglycan precursors containing the D-alanine-D-alanine terminal, and thus prevents cross linking of bacterial cell wall components. Telavancin anchors to the binding site with greater affinity and is approximately 10 times more potent than vancomycin.

A secondary mechanism, not seen with vancomycin, includes the ability of telavancin to change membrane potential and permeability in a concentration-dependent manner in Gram-positive bacteria.[4] The consequent disruption of the cell membrane results in cell lysis and rapid bactericidal activity.

*Pharmacokinetics & Pharmacodynamics*

At standard dosing of 10mg/kg, plasma concentrations increase linearly proportional to the dose of telavancin.[5] The observed half-life at this dose is 7 to 9 hours. Approximately 72% of the dose of telavancin is renally eliminated which warrants changes in dosing based on renal function.[7] Unlike vancomycin, clinical cure rates decline with a creatinine clearance ≤ 50ml/min.[8] Plasma protein binding of telavancin is high at approximately 90% with primary binding to serum albumin. Telavancin is metabolized hepatically to three hydroxylated metabolites. Mean plasma concentrations are 21% lower in patients with hepatic impairment compared to control ($p<0.05$) but the clinical significance of this finding is unclear. Although the metabolic pathway is not identified, cytochrome P450 enzymes do not appear to be involved. Consequently, mild-to-moderate hepatic impairment (Child-Pugh B)

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**Table 1. In vitro activity of telavancin against key gram-positive bacteria.**

| ANTIBACTERIAL/ORGANISM (# of isolates) | | $MIC_{90}$ RANGE (mg/ml) | Breakpoint |
|---|---|---|---|
| *S. aureus*: | Telavancin | 0.25 – 0.5 | ≤1mg/ml |
| methicillin susceptible (2515) | Vancomycin | 1 | ≤2mg/ml |
| *S. aureus*: | Telavancin | 0.25 – 0.5 | ≤1mg/ml |
| methicillin resistant (1669) | Vancomycin | 1 – 2 | ≤2mg/ml |
| *S. aureus*: | Telavancin | 1 | ≤1mg/ml |
| glycopeptide intermediate (50) | Vancomycin | 8 | ≤2mg/ml |
| *S. pneumoniae*: | Telavancin | 0.03 | NA |
| penicillin susceptible (371) | Vancomycin | 0.5 | ≤2mg/ml |
| *S. pneumoniae*: | Telavancin | 0.015 – 0.03 | NA |
| penicillin resistant (74) | Vancomycin | 0.5 | ≤2mg/ml |
| *E. faecalis*: | Telavancin | 0.5 – 1 | ≤1mg/ml |
| vancomycin susceptible (928) | Vancomycin | 2 | ≤4mg/ml |
| *E. faecalis*: | Telavancin | 8 – 16 | NA |
| vancomycin nonsusceptible (60) | Vancomycin | >512 | NA |
| *E. faecium*: | Telavancin | 0.25 | ≤1mg/ml |
| vancomycin susceptible (427) | Vancomycin | 1 | ≤4mg/ml |
| *E. faecium*: | Telavancin | 2 – 8 | NA |
| vancomycin nonsusceptible (352) | Vancomycin | >512 | NA |
| *S. pyogenes* | Telavancin | 0.06 | ≤0.12mg/ml |
| | Vancomycin | 0.5 | ≤1mg/ml |
| *S. agalactiae* | Telavancin | 0.06 | ≤0.12mg/ml |
| | Vancomycin | 0.5 | ≤1mg/ml |

Adapted from Dunbar et al. [5] and References 8, 13, and 26.

does not appear to affect the pharmacokinetics of telavancin and therefore dosing changes for hepatic insufficiency are not necessary.[9]

In vivo and in vitro animal studies of telavancin show concentration-dependent, bactericidal activity with the presence of significant post antibiotic effects. In an in vitro study conducted by Pace et al., telavancin showed a post antibiotic effect that lasted approximately 4 to 6 hours against strains of methicillin sensitive *S. aureus* (MSSA), MRSA, and VISA.[10] The best predictor of efficacy of telavancin is the ratio of the area under the curve (AUC) to minimum inhibitory concentration (MIC).

## *IN VITRO* SPECTRUM OF ACTIVITY

Telavancin is active against gram-positive organisms including vancomycin-resistant organisms, but is not effective in infections caused by gram-negative organisms (**Table 1**). Jansen et al. showed an $MIC_{90}$ range of telavancin, for MSSA and MRSA infections, between 0.06 mg/ml and 0.5 mg/ml.[11] In comparison, vancomycin MICs are approximately 2 to 4 times higher, linezolid are 4 to 80 times higher, and daptomycin has a MIC range that is 2 times higher than that of telavancin for the treatment of MSSA and MRSA infections. The $MIC_{90}$ and minimum bactericidal concentration ($MBC_{90}$) for community-acquired MRSA isolates is 0.5 mg/ml and 1 mg/ml respectively for telavancin.[12] For infections caused by VISA, telavancin has an $MIC_{90}$ of 1 mg/ml as compared to 8 mg/ml for vancomycin and 1 mg/ml and 2 mg/ml for daptomycin and linezolid respectively. Telavancin also exhibits good activity against Gram-positive anaerobes such as *Clostridium jeikeium* for cSSSI and *C. difficile*.

## FDA-APPROVED INDICATION FOR cSSTI

To date, the only FDA-approved indication for telavancin is complicated skin and skin structure infections (cSSSI). For telavancin to be effective, it must penetrate into the site of infection. After 3 to 4 days of treatment with 7.5 mg/kg daily, penetration into the abscess fluid compared to plasma levels was 0.79 and

**Table 2: Clinical studies evaluating telavancin.**

| STUDY | DESIGN | N | INCLUSION CRITERIA | STUDY LENGTH | RESULTS |
|---|---|---|---|---|---|
| **FAST II**[18] | • Randomized<br>• Double-blinded<br>• Active-control<br>• Parallel-group | • Telavancin (n=100)<br>• Standard Care (n=95)<br>  • Vancomycin (93%)<br>  • Antistaphylococcal PCN (7%) | • Age ≥ 18 years<br>• Diagnosis of cSSSI<br>  • presence of major abscess requiring surgical drainage<br>  • Deep, extensive cellulitis<br>  • an infected wound or ulcer<br>  • an infected burn | Pts treated for and evaluated at 7 – 14 days post administration of abx | Telavancin vs. standard therapy showed:<br>Cure rates were similar (82% vs. 85%; p=0.37<br>Eradication of pathogens were similar:<br>At EOT[a]: 89% vs. 77%; p=0.09<br>At TOC[b]: 94% vs. 83%; p=0.06<br>For MRSA 92% vs. 68%; p=0.04 |
| **ATLAS I**[19] | • Randomized<br>• Double-blinded<br>• Active-controlled<br>• Multinational | • Telavancin (n=426)<br>• Vancomycin (n=429) | • Age ≥ 18 years<br>• Diagnosis of cSSSI<br>  • Major abscess<br>  • Infected burn<br>  • Deep/extensive cellulitis<br>  • Infected ulcer<br>  • Wound infection<br>• Infection requiring 7-14 days of IV antibiotic therapy | Pts treated for and evaluated at 7 – 14 days post administration of abx | No difference between telavancin and vancomycin in clinical cure rates and microbiological eradication, including MRSA<br><br>Cure rates 87.9% vs. 86.5% (95% CI -3.6 – 6.3)<br>Microbiological eradication (89.5% vs. 85.9% (95% CI<br>-2.2 – 0.4)<br>Discontinuation due to ADR – 7% telavancin vs. 5% vancomycin |
| **ATLAS II**[20] | • Randomized<br>• Double-blinded<br>• Active-controlled<br>• Multinational | • Telavancin (n=502)<br>• Vancomycin (n=510) | • Age ≥ 18 years<br>• Diagnosis of cSSSI<br>  • Major abscess<br>  • Infected burn<br>  • Deep/extensive cellulitis<br>  • Infected ulcer<br>  • Wound infection<br>• Infection requiring ≥ 7 days of IV antibiotic therapy | Pts treated for and evaluated at 7 – 14 days post administration of abx | No difference between telavancin and vancomycin in clinical cure rates and microbiological eradication, including MRSA<br><br>Cure rates 77.1% vs. 73.7% (95% CI -1.9 – 8.7)<br>Microbiological eradication (76.9% vs. 74.8% (95% CI<br>-4.0 – 8.2) |

a = end of therapy visit
b= test-of-cure visit

0.82 respectively. The steady state AUC in the blister fluid was ~40% of that found in plasma and was sufficient to eradicate pathogens causing the infection.[14]

In a phase III randomized, parallel, double-blinded, active control trial, Strykewski et al compared the use of standard telavancin dosing (10 mg/kg every 24 hours) to vancomycin (1 g every 12 hours or individualized dosing based on standard practice at the site) for the treatment of cSSSI (**Table 2**).[15] Infections were defined by the presence of either cellulitis, major abscess requiring surgical drainage, infected wound or ulcer, or infected burn. Patients were required to have an active infection defined as 3 or more of the following signs or symptoms: erythema, heat and/or localized warmth, fluctuance, swelling and/or induration, pain and/or tenderness to palpitation, fever (temperature > 38$^{o}$c), WBC count > 10,000 cells/mm$^{3}$, or > 15% bands. The most common organisms cultured included *S. aureus*, MRSA, *E. faecalis,* other *Enterococcus* species, *S. pyogenes*, *S. agalactiae,* and some gram-negative organisms. The authors defined cure as resolution of clinically significant signs and symptoms or improvement in the extent of infection such that the patient no longer required antimicrobial treatment. The primary endpoint was clinical response at test-of-cure evaluation, 7-14 days after administration of the last dose.

The study demonstrated that telavancin is at least as effective to twice-daily vancomycin for the treatment of cSSSI. Telavancin demonstrated significant microbial eradication rates and overall therapeutic responses that support clinical response. When compared to vancomycin, response rates were similar across the most common types of infections and the most common gram-positive pathogens. The authors concluded that the use of telavancin is an alternative to vancomycin for the treatment of cSSSI caused by a variety of gram-positive microorganisms, including MRSA (**Table 2**).[15]

## Pending FDA Approval for Pneumonia

One clinically significant issue with vancomycin is reduced penetration into lung tissue. Telavancin does not have similar difficulties in penetrating the lungs.

Gotfried et al. conducted an in vitro study to assess the effects of pulmonary surfactant on telavancin and to identify the steady state concentrations achieved in epithelial lining fluid (ELF) and alveolar macrophages (AM). Patients received 3 consecutive days of 10mg/kg/dose with plasma levels obtained at 4- and 8-hours to reflect maximum intrapulmonary concentration, at 12 hours to represent the midpoint of the dosing interval, and at 24 hours to signify the end of the dosing interval. Telavancin concentrations in ELF and AM, at any interval, were greater than the $MIC_{90}$ of 0.5 mg/ml, which is considered clinically significant for MRSA infections.[16]

Pulmonary surfactant does not appear to affect the in vitro activity of telavancin against MRSA and *S. pneumonia*. However, the investigation failed to predict the effectiveness of telavancin for eradication of susceptible pathogens in pneumonia. Surfactant did not appear to alter the effects of vancomycin or ceftriaxone. The effects of surfactant on daptomycin was related to the concentration of surfactant (as the concentration of surfactant increased, the antibacterial activity of daptomycin decreased).[16]

Further in vivo studies need to be carried out to assess the complete efficacy of telavancin for use in pneumonia. ATTAIN I and II, phase III, randomized, double-blind trials assessing the efficacy of telavancin in HAP have been completed, however, results have not been published.[17]

## Dosing

For the treatment of cSSSI caused by susceptible strains of *S. aureus* (including MSSA and MRSA), *S. pyogenes, S. agalactiae, S. anginosus* group, or vancomycin susceptible *E. faecalis,* the usual dose is 10mg/kg once daily given over 1 hour for 7 to 14 days.[8] Because 72% of the telavancin dose is cleared renally, dosage adjustments are necessary for renal insufficiency (**Table 3**).

**Table 3. Renal adjustments.[8]**

| Creatinine Clearance | Dose | Frequency |
|---|---|---|
| >50ml/min | 10mg/kg | Every 24 hours |
| 30 – 50 ml/min | 7.5mg/kg | Every 24 hours |
| 10 – 29 ml/min | 10mg/kg | Every 48 hours |
| <10ml/min or hemodialysis | Insufficient evidence for use in this population | |

## SAFETY & TOLERABILITY

In the phase III ATLAS study, the most common treatment-emergent adverse events associated with telavancin were taste alterations, nausea, headache and vomiting, and foamy urine. ATLAS study showed that a QTc interval prolongation of 160 msec from baseline was infrequent and the number of patients with QTc interval prolongation was similar between both groups. Caution should be used when using telavancin in combination with other agents that cause QTc prolongation.[8]

## COST EFFECTIVENESS

The cost effectiveness of telavancin was determined during the ATLAS phase III clinical trial where infection related length of stay ($LOS_{IR}$), length of stay (LOS), and hospitalization costs ($COST_{IR}$) were compared between vancomycin and telavancin. No significant differences were noted in total LOS, treatment duration, $LOS_{IR}$, cost of additional antibiotics received, or $COST_{IR}$ between groups.[22] The main difference observed was the cost of vancomycin monitoring (median ~$51.25) as compared to telavancin ($0). The results may not be reproducible due to differences in healthcare systems, cost of acquisition, and medical practice.[22]

The cost of a 250 mg vial of telavancin is approximately $50.00 and the 750 mg vial is $150.00. Therefore, for a 70 kg patient the total daily cost of telavancin for a patient with normal renal function is $140 compared to approximately $20 per day for vancomycin administered 1 gm every 12 hours. Pharmacoeconomic analyses from ATLAS data suggest that telavancin may be more cost effective than vancomycin if telavancin can be acquired at similar prices as that of vancomycin, particularly in those with MRSA infections. However, such pricing of telavancin is likely years away.[22]

## SUMMARY

The increase in incidence of MRSA and VRE infections has led to the development of newer antimicrobial agents. Telavancin, a lipoglycopeptide that targets gram-positive microorganisms including MRSA and VRE, is an effective alternative to vancomycin for the treatment of cSSSI.[15] Although the efficacy of telavancin for pneumonia is not determined, in vitro studies suggest a possible beneficial effect but further studies are needed.[16] The major side effects include taste disturbance, foamy urine, and nephrotoxicity. Lastly, despite the increased acquisition cost, the lack of therapeutic monitoring may make telavancin more cost-effective versus vancomycin in MRSA infections.

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**Table 4. Incidence of treatment–emergent adverse drug reactions.**

| ADVERSE REACTION | TELAVANCIN | VANCOMYCIN |
|---|---|---|
| Nephrotoxicity | 15% | 7% |
| Taste disturbance (metallic or soapy) | 33% | 7% |
| Nausea | 27% | 15% |
| Vomiting | 14% | 7% |
| Foamy urine | 13% | 3% |
| Pruritis | | |
| Skin & appendages | 6% | 13% |
| Generalized | 3% | 6% |
| Increase in serum creatinine conc. | 0.5% | 2.5% |
| Rash | 4% | 5% |

Adapted from Corey et al. [21] and Atwood et al.[4]

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# VALTURNA® (ALISKIREN/ VALSARTAN): A NEW COMBINATION RAAS INHIBITOR

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Hypertension (HTN), known as the "silent killer," is common, affecting an estimated 73+ million Americans that require some type of antihypertensive treatment.[1] If left untreated, this disease can increase the risk of heart attack, heart failure, stroke, and kidney disease, and lead to other complications. Almost 30% of patients are not aware that they have HTN, and greater than 40% of patients who are aware are not on any kind of treatment.[2] Several classes of medications can be used in HTN treatment: diuretics, alpha and beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and the newest addition, direct renin inhibitors (DRIs). DRIs reduce blood pressure (BP) by suppressing renin effects and reducing plasma renin activity.[3] Valturna® (aliskiren/valsartan) was FDA approved on September 9, 2009 as the first combination DRI and ARB. It is manufactured by Novartis for the treatment of HTN in patients not controlled on monotherapy, substituted for the titrated components, or as initial therapy in patients who may need multiple medications to control their BP.[4] This article will review the efficacy, safety, and tolerability of aliskiren/valsartan.

## PHARMACOLOGY & PHARMACOKINETICS

Valturna® is a single tablet combination of aliskiren, a direct renin inhibitor, and valsartan, an angiotensin II antagonist at the $AT_1$ receptor subtype.

Aliskiren blocks the conversion of angiotensinogen to angiotensin (Ang) I. Suppressing Ang I decreases the formation of Ang II which functions as a negative inhibitory feedback to suppress renin release within the renin-angiotensin-aldosterone system (RAAS). Decreasing Ang II leads to an increase in plasma renin concentration.[5]

Valsartan works by antagonizing Ang II at the $AT_1$ receptor subtype. Four Ang II receptors have been identified: $AT_{1-4}$. However, only $AT_1$ and $AT_2$ receptors have been implicated in RAAS involvement in hypertension. Valsartan has a 20,000-fold greater affinity for the $AT_1$ receptor subtype.[6] Ang II is a potent vasoconstrictor and stimulates the synthesis and release of aldosterone. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of Ang II by selectively blocking the $AT_1$ receptors in the vascular smooth muscle and adrenal gland. Blocking the $AT_1$ receptors leads to a 2-3 fold increase in the circulating levels of renin and Ang II. The BP lowering effects are produced by antagonizing $AT_1$-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertonic responses. In addition, shifting Ang II action to the $AT_2$ receptor causes vasodilation.

The combination of aliskiren and valsartan blocks the RAAS at different sites leading to a complimentary mechanism in inhibiting the RAAS.[5]

The duration of action of both aliskiren and valsartan are about 24 hours, thus allowing for once daily dosing of aliskiren/valsartan. The rate and extent of absorption of each drug when administered in combination are the same as when administered as individual agents. Aliskiren inhibits the RAAS in a dose-dependent manner with the maximum reductions in Ang II observed within 1 hour after oral administration. The maximum antihypertensive effect of aliskiren occurs within 2 weeks of initiation. Absorption of aliskiren is poor and is further decreased by concomitant administration with high fat meals. When taken with food, the mean AUC is decreased by 76% and the Cmax is decreased by 88%.[6] Aliskiren is metabolized via CYP3A4 enzymes, though the extent of metabolism is unknown. One-fourth of the absorbed dose is excreted unchanged in the urine, and it is excreted unchanged in the feces via biliary excretion.

Valsartan has an onset of action of 2 hours and is rapidly absorbed regardless of concomitant food intake. Valsartan is metabolized to valeryl-4-hydroxy valsartan, the primary metabolite, which is inactive. The enzyme responsible for the metabolism of valsartan is unknown. It is also excreted as unchanged drug in the urine (13%) and feces (83%).[4,5,6] The pharmacokinetic (PK) profiles of aliskiren and valsartan are presented in **Table 1**.

## PHARMACOLOGY & PHARMACOKINETICS

*Renal Impairment*

Rate and extent of exposure (AUC and Cmax) of aliskiren in patients with renal impairment did not show a consistent correlation with the severity of renal impairment. No adjustment is needed in the starting dose in these patients. Similarly, there is no apparent correlation between renal function (measured by creatinine clearance [CrCl]) and exposure (measured

**Table 1. Pharmacokinetics of aliskiren and valsartan.**[5,6]

| | ALISKIREN | VALSARTAN |
|---|---|---|
| **Onset of action** | Maximum antihypertensive effect: Within 2 weeks | ~2 hours |
| **Duration of action** | Accumulation half-life: 24 hours | 24 hours |
| **Time to peak** | 1-3 hours (plasma) | 2-4 hours (serum) |
| **Bioavailability** | 2.5% | 25% |
| **Absorption** | Poor, decreased by high fat meals | Rapidly absorbed |
| **Metabolism** | Via CYP3A4; extent of metabolism unknown | To inactive metabolite |
| **Excretion** | Urine: 25% of absorbed dose unchanged<br>Feces: unchanged via biliary excretion | Feces (83%) & urine (13%) as unchanged drug |
| **Half-life elimination** | 16 – 32 hours | ~6 hours |

by AUC) to valsartan. In patients with mild-to-moderate renal impairment, no dosage adjustment is necessary. No studies have been performed in patients with severe renal impairment (CrCl <10 mL/min). Hemodialysis does not remove valsartan from the plasma.[4]

*Hepatic Impairment*

Aliskiren PKs were not significantly affected in patients with mild-to-moderate liver disease. Patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan compared to healthy volunteers; however, no dosage adjustment is needed in these patients.[4]

*Geriatric Populations*

PKs of aliskiren and valsartan were studied in patients ≥ 65 years. Exposure of aliskiren (measured by AUC) is increased in this population, but does not warrant adjustment of the starting dose. The exposure of valsartan is 70% higher and the half-life is 35% longer, but no dosage adjustment is necessary.[4]

## CLINICAL TRIALS

*Efficacy & Safety Studies*

Oparil, et. al. conducted an 8 week, randomized, double-blind, parallel-group, placebo controlled, dose escalation study to assess the BP lowering effects of dual renin system intervention with the combination of aliskiren and valsartan at their maximum doses. The study was conducted in men and women (n=1792) aged 18 years or older with stage 1–2 essential HTN (mean sitting diastolic blood pressure (MSDBP) of 95 to <110 mmHg). The primary outcome was change in MSDBP from baseline to week 8. One of the secondary outcomes included changes from baseline to week 8 in mean sitting systolic blood pressure (MSSBP).

Patients were randomly assigned to receive once daily aliskiren 150 mg, valsartan 160 mg, combination aliskiren/valsartan 150/160mg, or placebo for 4 weeks. After 4 weeks, all patients underwent a forced titration to double the dose of their treatment for another 4 weeks. Sitting BP was assessed at baseline and at weeks 2, 4, 6, and 8 (or at discontinuation) of the double-blind period.

At week 8, treatment with the combination of aliskiren and valsartan reduced MSSBP and MSSDBP from baseline significantly more than did aliskiren (p<0.0001) or valsartan (p<0.0001) monotherapy, or placebo (p<0.0001) (**Table 2** & **3**).

Monotherapy with aliskiren or valsartan provided significantly greater reductions in MSDBP and MSSBP

**Table 2. Least Squares Mean Changes in Mean Sitting Diastolic and Systolic Blood Pressure at Week 8.**[8]

| | **Placebo** (n=459) | **Aliskiren 300 mg** (n=437) | **Valsartan 320 mg** (n=455) | **Aliskiren/Valsartan 300/320 mg** (n=446) |
|---|---|---|---|---|
| Δ MSDBP, mmHg | -4.1 | -9.0* | -9.7* | -12.2† |
| Δ MSSBP, mmHg | -4.6 | -13.0* | -12.8* | -17.2† |

*p<0.0001 vs. placebo. †p<0.0001 vs. placebo, aliskiren, and valsartan.
LSM = least squares mean; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure

**Table 3. Summary of Clinical Trials Involving Aliskiren and Valsartan.**

| STUDY | DESIGN | DOSE | RESULTS |
|---|---|---|---|
| **Oparil, et al.**[8] (2007)<br><br>n = 1797 | • 8-week R, DB, PG, PCB-controlled, dose escalation study<br>• Primary outcome: Δ in MSDBP from baseline to week 8 endpoint | A 150 mg; V 160 mg; A/V 150/160 mg; or PCB x 4 weeks, followed by forced titration to A 300 mg; V 320 mg; A/V 300/320 mg or PCB x 4 weeks | At week 8 endpoint combo A/V 300/320 mg lowered MSDBP from BL by 12.2 mmHg significantly more than monotherapy (A 300 mg, 9.0 mm Hg decrease, *P*<0.0001; V 320 mg, 9.7 mm Hg decrease, *P*<0.0001), or with PCB (4.1 mm Hg decrease, *P*<0.0001) |
| **Chrysant, et al.**[9] (2008)<br><br>n = 601 | • 54-week, OL, MC<br>• Primary outcome: assess the safety of combo therapy; $K^+$ elevations were a predefined safety outcome | • A/V 150/160 mg x 2 weeks, followed by forced titration to A/V 300/320 mg x 52 weeks<br>• After 2 months from start of A/V 300/320 mg, HCTZ 12.5 mg (titrated to 25 mg) was permitted in pts w/ MSSBP ≥ 140 mmHg and/or MSDBP ≥ 90 mmHg at 2 consecutive visits | • 66.2% of patients reported at least one AE during the long-term combo treatment<br>• The most freq. reported AEs were: headache, dizziness, and nasopharyngitis<br>• 12 pts (out of 588; 2%) experienced $K^+$ levels > 5.5 mmol/L at any post-BL visit<br>• Overall, 4 pts (0.7%) were recorded with an AE of hyperkalemia |
| **Yarows, et al.**[10] (2008)<br><br>n = 581 | • Post-hoc analysis of an 8-week, R, DB, PCB-controlled, MC study in pts with stage 2 HTN<br>• Primary outcome: Δ in MSDBP from BL to week 8 endpoint | A 150 mg; V 160 mg; A/V 150/160 mg; or PCB x 4 weeks, followed by 4 weeks at double the initial dose | • A/V 300/320 mg reduced BP from BL by 22.5/11.4 mmHg at week-8 endpoint<br>• BP reduction with combo were sig. greater than with A 300 mg (17.3/8.9 mmHg, *P*<0.05), V 320 mg (15.5/8.3 mmHg, *P*<0.01), or with PCB (7.9/3.7 mmHg, *P*<0.0001). |
| **Pool, et al.**[11] (2007)<br><br>n = 1123 | • MC, R, PCB-controlled, 8-week trial<br>• Primary outcome: Δ from BL in MSDBP at endpoint | 3-4 week SB PCB run-in, then R in a modified factorial study design to receive once-daily, DB oral treatment with PCB, A (75, 150, or 300 mg), V (80, 160, or 320 mg), A/V combo (150/160 and 300/320 mg), or V/HCTZ (160/12.5 mg) | • Aliskiren monotherapy provides antihypertensive efficacy and PCB-like tolerability in pts with HTN<br>• A/V combo may provide additive BP-lowering effects with maintained tolerability |
| **Geiger, et al.**[12] (2008)<br><br>n = 641 | • R, DB, PG, active-control, dose-escalation study<br>• Primary efficacy variable: Δ in DBP from BL to week 8<br>• Primary objective: comparison at week 8 for the triple combination of<br>• A/V/HCTZ 300/320/25 mg with both double combinations of A/HCTZ 300/25 mg and V/HCTZ 320/25 mg | Following 4-week, SB HCTZ (12.5 mg for 1 week; 25 mg for 3 weeks), qualified pts (DBP ≥ 95 mmHg) were R to the equal ratio to receive A/V/HCTZ 150/160/25 mg x 4 weeks, 300/320/25 mg x another 4 weeks; A/HCTZ 150/25 mg x 4 weeks, 300/25 mg x another 4 weeks; V/HCTZ 160/25 mg x 4 weeks, 320/25 mg x another 4 weeks; or HCTZ 25 mg x 8 weeks | • A/V/HCTZ produced statistically significant additional reductions in SBP/DBP when compared with other groups (*P*<.001 vs. A/HCTZ; *P*<.01 vs. V/HCTZ; *P*<.001 vs. HCTZ)<br>• At week 8, reductions in SBP/DBP in the treatment groups were 22/16 (A/V/HCTZ), 15/11 (A/HCTZ), 18/14 (V/HCTZ), or 6/6 (HCTZ alone) mmHg<br>• A/V/HCTZ produced significantly better BP control (SBP/DBP <140/90 mm Hg; 66.7%) compared with other treatment groups (20.5%–48.7%, *P*<.001) |

Δ = change; A = aliskiren; AE = adverse event; A/V = aliskiren/valsartan; BL = baseline; BP = blood pressure; DB = double blind; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; HTN = hypertension; MC = multicenter; MSDBP/SBP = mean sitting diastolic blood pressure/systolic blood pressure; OL = open-label; PCB = placebo; PG = parallel group; pts = patients; R = randomized; SB = single-blind; SBP = systolic blood pressure; V = valsartan

than did placebo at week 8 endpoint (all p<0.0001). Combination therapy provided additional reductions of 4.2/3.2 mmHg over aliskiren monotherapy and 4.4/2.5 mmHg over valsartan monotherapy.

Adverse events occurred at similar frequencies in both monotherapy groups, the combination group, and placebo. The most common adverse events in the aliskiren, valsartan, and the combined aliskiren/valsartan treatment groups were headache, nasopharyngitis, and dizziness (**Table 4**).

The proportion of patients with a serum $K^+$ concentration over 5.5 mmol/L at any point after baseline was higher in the combination group (4.5%) than either monotherapy group (aliskiren 4%; valsartan 4%) or placebo group (4%). A clinically relevant increase in serum creatinine (> 2.0 mg/dL) was seen in four patients receiving combination treatment, two patients receiving valsartan, and one patient receiving aliskiren. The increases were not associated with a notable increase in the blood urea nitrogen. Neither of the serum $K^+$ nor creatinine concentration increases was associated with AEs or led to patient discontinuation from the study.[8]

Chrysant et. al. conducted a six month interim analysis on the long-term safety, tolerability, and efficacy of aliskiren used in combination with valsartan for HTN. In this 54-week, open-label, multicenter study, 601 patients with HTN received a combination of aliskiren/valsartan 150/160 mg for 2 weeks followed by forced titration to aliskiren/valsartan 300/320 mg once daily. The addition of optional hydrochlorothiazide (HCTZ) was allowed from week 8 for inadequate BP control (≥ 140/90 mmHg). The primary objective was to assess the safety of combination therapy; potassium elevations were a predefined safety outcome.

At the 6 month cut-off date, 512 patients (85.2%) were still on study treatment, and 192 patients (31.9%) had received at least one dose of HCTZ during this period. Combination therapy (aliskiren/valsartan 300/320 mg with or without HCTZ) was generally well tolerated, and the most commonly reported AEs

**Table 4. Safety and Tolerability of Study Treatments.**[8]

| | Placebo* (n=458) | Aliskiren (n=437) | Valsartan (n=455) | Aliskiren/Valsartan (n=446) |
|---|---|---|---|---|
| **AE** | | | | |
| Any AE | 168 (37%) | 149 (34%) | 167 (37%) | 156 (35%) |
| Any Serious AE | 5 (1%) | 8 (2%) | 6 (1%) | 3 (0.7%) |
| Discontinuation due to AE | 10 (2%) | 11 (3%) | 11 (2%) | 7 (2%) |
| **Most Frequent AEs (≥ 2% in Any Group)** | | | | |
| Headache | 41 (9%) | 14 (3%) | 25 (5%) | 19 (4%) |
| Nasopharyngitis | 9 (2%) | 16 (4%) | 20 (4%) | 12 (3%) |
| Dizziness | 9 (2%) | 8 (2%) | 11 (2%) | 8 (2%) |
| Fatigue | 11 (2%) | 6 (1%) | 7 (2%) | 7 (2%) |
| Nausea | 41 (9%) | 14 (3%) | 25 (5%) | 19 (4%) |
| **Laboratory Abnormalities** | | | | |
| Serum Potassium† | | | | |
| < 3.5 mmol/L | 17 (4%) | 11 (3%) | 20 (4%) | 12 (3%) |
| > 5.5 mmol/L‡ | 12 (3%) | 7 (2%) | 7 (2%) | 18 (4%) |
| ≥ 6.0 mmol/L | 6 (1%) | 4 (1%) | 5 (1%) | 2 (0.5%) |
| Creatinine§ | | | | |
| > 176.8 µmol/L (2.0 mg/dL) | 0 | 1 (0.2%) | 2 (0.4%) | 4 (0.9%) |
| Blood Urea Nitrogen | | | | |
| > 14.3 mmol/L | 0 | 1 (0.2%) | 1 (0.2%) | 0 |

Data are n (%); AE = adverse event

*One randomized patient did not take double-blind medication before discontinuation.

†n=445 for placebo, 416 for aliskiren, 443 for valsartan, 424 for aliskiren/valsartan.

‡Of the 18 patients with increases in serum potassium >5.5 mmol/L during double-blind treatment, 13 had potassium concentrations within the normal range at the end of the study without the need for treatment disruption.

§n=446 for placebo, 417 for aliskiren, 445 for valsartan, 426 for aliskiren/valsartan.

**Table 5. Retail Pricing for a 1 month supply (30 tablets).**

| | AVERAGE | RANGE |
|---|---|---|
| **Tekturna® (aliskiren)** | | |
| 150 mg | $92.02 | $89.99 – $94.49 |
| 300 mg | $119.32 | $118.99 – $119.99 |
| **Diovan® (valsartan)*** | | |
| 160 mg | $95.32 | $86.99 – $100.99 |
| 320 mg | $120.15 | $107.49 – $126.99 |
| **Valturna® (aliskiren/valsartan)** | | |
| 150/160 mg | $90.15 | $82.99 – 93.99 |
| 300/320 mg | $109.32 | $103.99 – $113.99 |

Prices were obtained from three community pharmacies in Gainesville, FL.
* Valsartan is expected to become available generically in September 2012 when the patent expires

were headache, dizziness, and nasopharyngitis. Serum potassium elevations > 5.5 mmol/L occurred in 10 patients receiving aliskiren/valsartan and 2 patients receiving aliskiren/valsartan/HCTZ. Only one patient treated with aliskiren/valsartan exhibited potassium levels ≥ 6.0 mmol/L during this period. Aliskiren/valsartan combination therapy (with or without HCTZ add-on) provided mean reductions in MSSBP/DBP from baseline of 22.3/14.4 mmHg at the 6-month endpoint. Combination therapy (aliskiren/valsartan) provided effective BP lowering which was maintained over the 6 month treatment period.[9]

*Stage II Hypertension Subgroup Analysis*

Yarows et. al. conducted a *post-hoc* analysis on the efficacy of aliskiren/valsartan in reducing BP in patients with stage 2 HTN. This subgroup analysis comes from the previous study conducted by Oparil, et al. Aliskiren/valsartan 300/320 mg reduced MSSBP/DBP from baseline by 22.5/11.4 mmHg after 8 weeks. BP reductions with combination therapy were significantly greater than with aliskiren 300 mg (17.3/8.9 mmHg, $P<0.05$), valsartan 320 mg (15.5/8.3 mmHg, $P<0.01$), or with placebo (7.9/3.7 mmHg, $P<0.0001$). BP control rates (<140/90 mmHg) were also significantly higher ($P<0.05$) with aliskiren/valsartan 300/320 mg (29.8%) compared with either aliskiren 300 mg (19.0%) or valsartan 320 mg (13.8%) monotherapy, or placebo (8.9%). All treatments were generally well tolerated. The authors concluded that aliskiren/valsartan combination therapy is an appropriate option for management of BP in patients with stage 2 HTN.[10] See **Table 3** for a summary of the clinical trials involving aliskiren and valsartan.

## DRUG INTERACTIONS

Aliskiren is a substrate of P-glycoprotein (Pgp); concurrent use of Pgp inhibitors may increase absorption.[5] Cyclosporine is a highly potent Pgp inhibitor. Concomitant administration of cyclosporine and aliskiren results in a 2.5-fold increase in Cmax and 5-fold increase in AUC of aliskiren; therefore, it is not recommended.

Concomitant use of $K^+$ sparing diuretics (spironolactone, triamterene, amiloride), $K^+$ supplements, or salt substitutes containing $K^+$ with valsartan may lead to increases in serum $K^+$. In heart failure patients, valsartan can lead to increases in serum creatinine.[4]

## DOSING & ADMINISTRATION

The recommended doses of aliskiren/valsartan are 150/160 mg daily or 300/320 mg daily. For patients initiating therapy with aliskiren/valsartan, the recommended starting dose is 150/160 mg daily. The dose can be titrated up to 300/320 mg once daily after 2-4 weeks of therapy.

Patients who are currently receiving either aliskiren or valsartan alone may be switched to combination therapy if their BP is not adequately controlled on monotherapy. The recommended starting dose is 150/160 mg daily. Similarly, patients receiving aliskiren and valsartan as separate pills may be switched to single tablet aliskiren/valsartan containing the same component doses for convenience.

Aliskiren/valsartan can be administered with or without food and should be administered at the same time each day.[4]

## COST

The average retail prices, for a one month supply (30 tablets), of aliskiren, valsartan, and aliskiren/valsartan are shown in **Table 5**. The individual components of Valturna®, aliskiren and valsartan, are not currently available generically. However, the patent on valsartan is set to expire in September 2012, making generic valsartan available in approximately 2-2.5 years. Aliskiren is marketed as Tekturna®, and valsartan is marketed as Diovan®.

## SUMMARY

Aliskiren/valsartan, a combination direct renin inhibitor and angiotensin receptor blocker, is one of the newest treatment options for hypertension. It is a therapeutic, cost-effective medication, compared to its individual components, for patients initiated on dual therapy or whose hypertension is not controlled with a single agent. Combination therapy is more effective in reducing blood pressure than monotherapy with either medication. It is dosed once daily with few adverse reactions. However, the efficacy of dual RAAS inhibition has not been shown to be superior compared to a single RAAS inhibitor plus another antihypertensive agent (i.e. diuretic, CCB, etc.). Results of the recent ONTARGET trial suggest little additional advantage from the combination of an ARB and an ACE -I over either agent alone when used in patients who have vascular disease or high-risk diabetes, but do not have heart failure.[12] Furthermore, this combination can be associated with an increased risk for AEs.[12] Until more data become available with dual RAAS inhibition using direct renin inhibitors, potential candidates for aliskiren/valsartan should be carefully selected to minimize the potential for adverse effects.

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