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APPLICATION NUMBER

NDA 21-283/S011

Medical Review(s)

NDA 21-283, S-011

Drug Name: Diovan ® (valsartan)
Sponsor: Novartis
Indication: Improve survival following myocardial infarction

Primary Medical Reviewer: Shari L. Targum, M.D.
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Clinical Review for NDA 21-283, S-011

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Please see Sections VI A. Integrated Summary of Efficacy and X, Conclusions and Recommendations. Since VALIANT was an active-controlled study, without a placebo control, the issues of non-inferiority and effectiveness of valsartan depend on analysis of margins and choice of historical study as a basis for captopril (and placebo) effect. The conclusions of the medical reviewer are based on acceptance (or rejection) of assumptions and corresponding analyses of valsartan treatment effect (see Section X, Conclusions and Recommendations). Since different analyses have yielded different outcomes (see medical-statistical review, Table 39), and the reviewer is unsure which analysis to choose, the reviewer will recommend against approval, arguing that the weight of evidence does not support approval.
However, the reviewer acknowledges that valsartan results are numerically similar to captopril for primary, secondary and tertiary endpoints.

Since there is no benefit for the valsartan-captopril combination, as well as increased safety issues (e.g., highest incidence in pre-specified adverse events, highest discontinuation rate), there appears to be no reason to use the valsartan-captopril combination in this patient population.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None at this time.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical program involved one active-controlled study (VALIANT) of valsartan (up to 160 mg twice daily), captopril (up to 50 mg three times daily), and a combination valsartan (up to 80 mg twice daily)-captopril (up to 50 mg three times daily) group in patients following myocardial infarction (MI) with either clinical or radiologic signs of heart failure and/or evidence of left ventricular (LV) systolic dysfunction. The primary endpoint was all-cause mortality (time to death). A total of 14,702 patients were randomized into this study. The primary objectives were: 1. superiority of valsartan to captopril in reduction of mortality; 2. superiority of combination therapy to captopril in reduction of mortality; and 3. if superiority could not be demonstrated, then non-inferiority of valsartan to captopril in reduction of mortality.

B. Efficacy

Results of the primary, secondary and tertiary endpoints of this study were numerically similar between valsartan and captopril and no superiority was demonstrated (i.e., objectives #1 and 2 were not met). The main efficacy issues involved : 1. the question of non-inferiority and 2. how efficacy of valsartan could be demonstrated in the absence of a placebo control. If one uses preservation of > 50% of captopril effect to establish efficacy for valsartan, then the conclusions are dependent on the choice of analysis in addition to the choice of historical study used to establish captopril effect. For further details please see Section VI A (Integrated Review of Efficacy) as well as the medical-statistical review.

C. Safety

The mean (SD) exposure to study drug was 612.8 (353.4) days for valsartan, 585.7 (365) days for valsartan + captopril, and 599.2 (358.3) days for captopril. The median exposure was 665 days for captopril and 672 days for valsartan.

For the primary analysis population, the mean (709.1-711.6 days; SD 309-312) and median (739-743 days) time in the trial (including days on and off drug and regardless of permanent discontinuation) were similar across the three treatment groups. The frequency distribution (time on trial) also was similar across treatment groups. The safety population (valsartan N=4885, combination N=4862, captopril N=4879) consisted of those patients receiving at least one dose of study drug.

The medical reviewer concludes that the safety testing in the submission is likely sufficient, in terms of exposed patients and length of follow-up, in its ability to uncover important safety problems within the time frame of the study.

The safety findings in VALIANT were, by and large, consistent with side effects that appear in current labeling for valsartan (i.e., hypotension, increased creatinine) and captopril (i.e.,cough).

The highest incidence of pre-specified adverse events , in addition to discontinuation, down-titration and temporary discontinuation rates were seen in patients in the combination valsartan-captopril treatment group.

D. Dosing

VALIANT was not designed to explore relationship of different doses with the primary endpoint. The only dosing issue relates to the scored 40 mg tablet, which is discussed in the biopharmaceutics and chemistry reviews.

E. Special Populations

Baseline demographics in the VALIANT study population included about 31-32% females and about 51-52% patients aged 65 and older. The sponsor's investigation into the gender and age subgroups appear adequate. About 93-94% were Caucasian; insufficient numbers of non-Caucasians were studied to permit an adequate assessment of efficacy/safety.

For the primary endpoint (all-cause mortality) a higher event rate was seen, in all treatment groups, in the elderly or female subgroups. No unusual gender-related safety signal was seen. With regard to the elderly, an increased incidence of hypotension NOS was seen in the elderly subgroup, with the highest incidence in the valsartan group.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor, Novartis, has submitted a supplement to the valsartan (Diovan®) NDA 21-283 (S-011). The proposed indication is to improve survival following myocardial infarction (MI) in clinically stable patients with sign, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction. The sponsor has proposed a valsartan starting dose of 20 mg twice daily, with up-titration to 40, 80 and 160 mg twice daily to the highest tolerated dose.

To support the proposed indication, the sponsor has submitted the VALIANT study, an active-controlled trial of valsartan (up to 160 mg twice daily), captopril (up to 50 mg three times daily), and a combination valsartan (up to 80 mg twice daily)-captopril (up to 50 mg three times daily) in patients following MI with either clinical or radiologic signs of heart failure and/or evidence of left ventricular (LV) systolic dysfunction. The primary efficacy parameter was all-cause mortality (time to death). The three primary objectives of this study were: 1. superiority of valsartan monotherapy to captopril monotherapy; 2. superiority of the valsartan-captopril combination to captopril monotherapy; 3. If valsartan monotherapy was not shown to be superior as in objective #1, then to demonstrate that valsartan monotherapy is at least as effective as captopril monotherapy in reduction of total mortality post-MI.

Valsartan, an angiotensin receptor antagonist (ARB) is currently approved, in once daily doses of 80-320 mg, for the management of hypertension. Valsartan is also indicated, in doses of 40-160 mg twice daily, for the treatment of congestive heart failure (NYHA Class II-IV) in patients unable to tolerate ACE inhibitor therapy.

B. State of Armamentarium for Indication(s)

Three angiotensin converting enzyme (ACE) inhibitors, captopril, ramipril and trandolapril, are approved to improve survival following MI in patients with either left ventricular dysfunction (captopril, trandolapril) or clinical signs of heart failure (ramipril).

In addition, lisinopril is approved to improve survival in hemodynamically stable patients post-myocardial infarction.

To date, no ARB is approved to improve survival in post-MI patients.

C. Important Milestones in Product Development

In a 1998 Agency review of the VALIANT protocol, the primary (superiority) analysis was felt acceptable. However, the Agency did not agree with the non-inferiority boundary of 1.13, proposed by the sponsor, based the upper confidence interval of the hazard ratio. A boundary of 1.09 was proposed at the time, based on the upper confidence limit (95%) from the analysis of the 3 index trials as estimate of the treatment effect whereas the sponsor used the point estimate.

D. Other Relevant Information

To the best of this reviewer's knowledge, valsartan has not been approved in other countries for the proposed indication (survival benefit post-MI).

E. Important Issues with Pharmacologically Related Agents

The OPTIMAAL study was an active-controlled event-driven study of losartan (up to 50 mg once daily) vs. captopril (up to 50 mg three times daily) in patients with a new Q-wave MI and heart failure. In this 5477 patient study, the all-cause mortality rate was 18.2% for patients randomized to losartan and 16.4% for patients randomized to captopril, favoring captopril. For further details, please see the medical-statistical review.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

According to the biopharmaceutics reviewer (Dr. Nhi Beasley), the main clinical pharmacology and biopharmaceutics issue was that the initial dose in the VALIANT study was 20 mg twice daily and the lowest marketed strength was a 40 mg unscored tablet. The sponsor, therefore, has proposed to replace the unscored 40 mg tablet with a scored version. The approval of the new ovaloid 40 mg scored tablet is based on in vitro dissolution data, and the two tablets have a similar dissolution profile. The scored 40 mg tablet is bioequivalent to the unscored 40 mg tablet. The reviewer notes that the 20 mg valsartan capsule used in VALIANT is not ——— to the current 40 mg tablet; therefore, a biowaiver cannot be granted for the 20 mg dose. However, few patients were taking 20 mg twice daily at the end of the trial. ——— since these studies were not relevant to the main issue, they were not reviewed.

According to the chemistry reviewer, the main issues were: 1. change in tablet shape; 2. addition of a score; 3. application of an additional ——— of the film coat to the tablet. At the time of this review, there are no outstanding chemistry issues. An environmental assessment was completed with a finding of no significant impact.

No pharmacology/toxicology data were reviewed for this efficacy supplement.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Valsartan is an approved drug and its pharmacokinetics have been previously characterized.

According to current labeling, valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Absolute bioavailability for valsartan is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

B. Pharmacodynamics

VALIANT was a dose-titration study, where the goal was to titrate patients to Step 4 (the maximum dose). Therefore, no conclusions will be drawn concerning a relationship between valsartan doses and outcomes.

IV. Description of Clinical Data and Sources

A. Overall Data

The major source of data used in the review came from the VALIANT clinical trial. An additional two bioavailability studies were submitted to the biopharmaceutics reviewer. Where applicable, the reviewer used literature sources and current product labeling. In addition, for the comparison of prior ACE inhibitor studies, the reviewer used the available NDA reviews.

B. Tables Listing the Clinical Trials

N/A

C. Postmarketing Experience

Valsartan is not approved in the treatment of post-MI patients. Hence, there is no postmarketing experience for valsartan or other ARB.

D. Literature Review

The sponsor provided hyperlinks to several appropriate literature references, including background materials and publications relating to ACE inhibitor studies in the post-MI population. The reviewer also conducted separate literature searches pertaining to ACE inhibitor post-MI studies.

V. Clinical Review Methods

A. How the Review was Conducted

The VALIANT study formed the basis of the medical-statistical review. Since study analysis depended on non-inferiority margins, the reviewer also compared the studies that formed the basis for estimating the captopril effect.

B. Overview of Materials Consulted in Review

The reviewer analyzed the electronically submitted NDA supplement as supplied by the sponsor. Where applicable, the reviewer also utilized product labeling, prior NDAs and published clinical trials in order to obtain data for pertinent ACE inhibitors. A literature search was used to obtain information regarding the OPTIMAAL study, an active-controlled ARB vs. captopril study in patients following myocardial infarction, in addition to other information concerning ACE inhibitors and ARBs.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) audit processes were solicited for selected sites.

A Clinical Inspection Summary, dated May 25, 2004, was received from DSI for three inspected sites in the United Kingdom, Norway, and Russia, respectively. These inspections revealed nothing that would be expected to impact the validity of the data submitted and the data were felt to be acceptable.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The VALIANT appears to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

About 99-100% of principal investigators completed financial disclosure information (some missing information was noted with sub-investigators). Two investigators (sites 9603 and 8801) disclosed financial arrangements with the sponsor. Given that this study enrolled patients from 931 sites, the reviewer

concludes that it is highly unlikely that these financial arrangements influenced the outcome of the study.

VI. Integrated Review of Efficacy

Please see the medical-statistical review for further details.

A. Brief Statement of Conclusions

Analysis results for the primary endpoint – all-cause mortality (primary analysis population; reviewer's analysis)

	Valsartan vs. Captopril (N=4904) (N=4909)			Valsartan+Captopril vs. Captopril (N=4885) (N=4909)		
	No. of deaths (%)[1] valsartan/captopril	Hazard ratio CI[2]	p-value	No. of deaths (%)[1] combo/captopril	Hazard ratio CI[2]	p-value
All-cause mortality	979 (19.9) / 958 (19.5)	1.001 (0.902, 1.111) (0.904, 1.108)[4]	0.98[3]	941 (19.3)/ 958 (19.5)	0.984 (0.886, 1.093)	0.73[3]

Source: Table 35, medical-statistical review (also see Table 15, for the one-sided non-inferiority analysis provided by the sponsor)

1. Percent = raw estimate of mortality rate: (number of deaths / number of patients in each group)*100%
2. Hazard ratio = valsartan or combo / captopril. The two-sided CI (97.82%) has been adjusted for all interim analyses
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference
4. Two-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril.

1. Superiority of valsartan to captopril was not demonstrated.
2. Superiority of the valsartan-captopril combination to captopril was not demonstrated.
3. With respect to the primary, secondary and tertiary endpoints, results were numerically similar between captopril and valsartan.
4. The sponsor's non-inferiority margins were based on results from SAVE, AIRE and TRACE. However, the placebo mortality rate was higher in the TRACE population (medical-statistical review, Table 36). In addition, a comparison of the three studies showed differences in trial design and population (medical-statistical review, Table 37). Only SAVE used captopril as active treatment vs. placebo.
5. Can one conclude that valsartan is effective? If this conclusion is based on the premise that valsartan retains > 50% of the captopril effect, then results depend on analysis method and the historical trials used to ascertain captopril effect.

Results of non-inferiority analyses for retention of >50% captopril (C) by valsartan (V)

Historical trials	Method of non-inferiority analysis	Non-inferiority analysis result	Conclude that V retains >50% of C effect?
SAVE, AIRE, TRACE combined	Worst CI limit	(0.904, 1.108)* contains 1.08	Fail
	Synthesis	(0.890, 1.125)** rules out 1.13	Succeed
SAVE, AIRE combined	Worst CI limit	(0.904, 1.108)* contains 1.067	Fail
	Synthesis	(0.881, 1.137)** rules out 1.140	Succeed

SAVE only	Worst CI limit	(0.904, 1.108)* contains 1.02	Fail
	Synthesis	(0.866, 1.157)** contains 1.111	Fail

Source: Table 39, medical-statistical review.

*With worst CI limit method, 97.47% confidence interval is compared to the conservative margin

**With synthesis method, inflated interval wider than 97.47% confidence interval is compared to the point-estimate margin (see review and Appendix for details)

VII. Integrated Review of Safety

Please see the medical-statistical review for further details.

A. Brief Statement of Conclusions

1. The most common serious adverse event in all treatment groups was heart failure.
2. The highest discontinuation, down-titration and temporary discontinuation rates were seen in patients in the combination valsartan-captopril treatment group.
3. The highest incidence in pre-specified adverse events occurred in the combination valsartan-captopril treatment group (medical-statistical review, Table 28).
3. No gross imbalances were seen across treatment groups in serious adverse events, hospitalizations, blood pressure or heart rate.
4. Compared to captopril, there were higher rates of renal dysfunction (prespecified adverse event) in the valsartan group. In addition, compared to captopril, there was a higher discontinuation rate due to hypotension in the valsartan group (either alone or in combination). There were higher rates of down-titration due to hypotension or increased creatinine in the valsartan group.
5. Compared to valsartan, there was a higher discontinuation rate due to cough in the captopril group (either as monotherapy of in combination).
6. Hypotension and increased creatinine appear in current valsartan labeling; cough is a known side effect of captopril use. No unlabeled or unusual safety findings were identified in this submission.
7. The incidence of angioedema was 0.9-1.0% across treatment groups with no differences across groups.

VIII. Dosing, Regimen, and Administration Issues

VALIANT was not designed to explore a relationship between different doses and the primary endpoint.

The only other dosing issue relates to the 20 mg dose (20 mg twice daily was the lowest valsartan dose: Step 1) and the issue of a biowaiver. However, patients in VALIANT were up-titrated, as tolerated to the maximum dose. The mean titration in the study was to about Step 3 (i.e., valsartan 80 mg twice daily). Please see Figure 1 and Table 14 (medical-statistical review) for further details.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The VALIANT study population was about 31-32% female, including about 1500 randomized females per treatment group. The sponsor provided gender subgroup analyses of efficacy and safety in the submission. Compared to males, there is a higher event rate, across all treatment groups, in the female subgroup. The rate of all-cause mortality (valsartan vs. captopril) appears similar across treatment groups. The hazard ratio appears numerically more favorable for valsartan in the female subgroup, and more favorable for captopril in the male subgroup (with confidence intervals including 1.0); however, no significant differences between valsartan and captopril were seen.

Rates of all-cause mortality in subgroups (primary analysis population):

Subgroup	Valsartan event rate n/N (%)	Val + Cap event rate n/N (%)	Captopril event rate n/N (%)	Val vs. Cap HR (95% CI)
Gender				
Male	620/3365 (18.4)	598/3395 (17.6)	594/3373 (17.6)	1.029 (0.920, 1.152)
Female	359/1544 (23.3)	343/1490 (23.0)	364/1536 (23.7)	0.954 (0.824,1.103)

Source: Table 18 (combined medical-statistical review)

In terms of safety, a higher incidence was seen, across all treatment groups, of symptomatic hypotension in males and renal dysfunction and dry cough in females. Females in the combination (valsartan-captopril) group had the highest incidence of dry cough; males in the combination group had the highest incidence of symptomatic hypotension (for further information, please see Tables 31 and 32 in the combined medical-statistical review).

In summary, the sponsor's investigation of gender effects appears adequate. In general, the incidence of adverse events by gender appears to mirror the adverse events (and discontinuation rates) by treatment group, with the highest gender-related adverse events seen in the combination valsartan-captopril group. In the comparison of valsartan to captopril, no unusual gender-related safety signal has been identified.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

About 52-53% of the VALIANT study population was 65 years and older. The sponsor presented analyses of efficacy and safety subdivided by patients under <65 years and ≥ 65 years old. The sponsor's analyses of efficacy and safety by age appear adequate.

Rates of all-cause mortality in subgroups (primary analysis population):

Subgroup	Valsartan event rate n/N (%)	Val + Cap event rate n/N (%)	Captopril event rate n/N (%)	Val vs. Cap HR (95% CI)
Age				
< 65 years	268/2313 (11.6)	273/2370 (11.5)	275/2305 (11.9)	0.935 (0.79, 1.106)
≥ 65 years	711/2596 (27.4)	668/2515 (26.6)	683/2604 (26.2)	1.026 (0.924,1.140)

Source: Table 18 (combined medical-statistical review)

A higher event rate is seen, across all treatment groups, in the older population compared with patients under 65 years old. While the valsartan-captopril hazard ratio analysis is numerically favorable toward valsartan in the < 65 year subgroup, and favorable toward captopril in the ≥ 65 subgroup, no significant differences are seen between valsartan and captopril.
In terms of safety, an increased incidence of hypotension NOS (not otherwise specified) was seen in the elderly subgroup, with the highest incidence in the valsartan group.
(medical-statistical review, Table 29). In addition, the incidence of renal dysfunction appears higher in the elderly subgroup (about 3 times the rate in the younger population) and highest in the combination arm (medical-statistical review, Table 30). Several serious adverse events, including cardiac failure, MI, cardiac arrest, cerebral infarction and cerebrovascular accidents, occurred more frequently in the ≥ 65 year group, regardless of treatment.

There were insufficient numbers of non-Caucasians randomized; therefore, conclusions cannot be drawn about the impact of race on efficacy or safety.

C. Evaluation of Pediatric Program

No patient under 18 years old was studied in this submission.
The sponsor received a Written Request, dated June 18, 2003, for pediatric studies of valsartan for the treatment of hypertension. The sponsor is seeking a waiver for the treatment of post-MI patients as the necessary studies will be impossible or highly impractical because the number of pediatric patients with myocardial infarctions will be small.

D. Comments on Data Available or Needed in Other Populations

Because the data are limited, it would be of interest to conduct further study in non-Caucasian populations.

X. Conclusions and Recommendations

A. Conclusions

The medical reviewer, while acknowledging that the primary, secondary and tertiary efficacy results for valsartan and captopril are numerically similar in this large study, concludes that the weight of evidence for valsartan, using preservation of over 50% of captopril effect, is too dependent on the kind of analysis and historical studies used to predict captopril (and therefore placebo) effect. It would have been reassuring if all analyses and historical study choices pointed toward one result; however, this is not the case. Consequently, this reviewer acknowledges some difficulty in choosing which assumptions to accept or reject and interpreting the results. If the reviewer adopts a conservative position, assuming that over 50% of captopril effect is needed to prove valsartan efficacy, and using the captopril study (SAVE) to predict captopril effect (notwithstanding the issues surrounding use of an older historical control), then results from VALIANT do not support efficacy of valsartan. However, if one chooses to accept different assumptions, then it is possible that one might reach other conclusions.

Given that there is no current treatment alternative to ACE inhibitors, it would be attractive to offer valsartan in the VALIANT population if some basis for benefit could be established vs. risk of therapy.

B. Recommendations

None at this time.

XI. Appendix

The reader is referred to the combined medical-statistical review for a detailed discussion of the VALIANT study.

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/s/

Shari Targum
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