# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 20-818

## ADMINISTRATIVE DOCUMENTS
## CORRESPONDENCE

FEB 20 1998

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

**Memorandum**

**DATE** : FEB 20 1998

**FROM** : Director, Division of Cardio-Renal Drug Products, HFD-110

**SUBJECT**: Approvable, NDA 20-818, Fixed-Dose Combination of valsartan and HCTZ, Novartis Pharmaceuticals Corporation

**TO** : NDA File

A pretty straight forward approval. For change from baseline, trough, sitting diastolic blood pressure (the predeclared principal endpoint), a formal p value of <0.0001 (study 301, 90 to 100 patients/cell for superiority or the combination over each component and placebo, in a factorial trial) is persuasive enough. Study 301 survives Bonferoni correction for each comparison ( the Hochberg's MC procedure; a kind of Bonferoni) for each of the doses tested gives a p <0.0099 for the statement that at each dose level studied both ingredients contribute to the effect of the combination and that all doses tested give results greater than did placebo.

Cleft palate. I have elected not to follow up on the cleft palate, as suggested in Dr. Ganley's memorandum of February 4, 1998. The rat teratology studies examined 111 rat litters (divided among 5 groups, control, 0:187.5, 50:15.6, 200:62.5, and 600:187.5, mg/kg, for hydrochlorothiazide:valsartan, respectively. Two (2) litters in the 200:62.5 mg/kg group had evidence of cleft palate, all other (including the highest dose group had no evidence of cleft palate in any litter. Without further exploration, I reject this as a signal that needs attention.

Novartis, in a submission dated February 13, 1998, document that historical controls have similar rates and therefore the rates of cleft palate should be accepted as within the range of normal.

Dose Ranges. The maximum dose of valsartan studied was 160 mg, once-a-day along with 25 mg of HCTZ (94 patients for about 53 days). This combination produced the largest change from baseline, -12.1 mm Hg (placebo subtracted). In the appropriate model choice (Dr. Nuri's review; $E_{Max}$), the effect was continuing to rise at the greatest doses actually studied. So, blood pressure effects would have been greater had 320/25 or 320/50 been studied.

Valsartan can be administered at doses up to 320 mg per day. It is not clear why 160 mg was the greatest dose studied. So there is somewhat of a dilemma here. Should the combination product be allowed to dose up to 320/25, in spite of never having been studied? Such dosing would be possible, using 2 of the 160/12.5 mg dosage strengths that are to be marketed. I think the answer to the question is yes indeed, provided it is being used as a replacement for doses that were found during individual entity titration.

Serum Potassium. The following table shows the percent of patients that had a > 20% drop in serum potassium by treatment group; the number of patients is about 90 per group.

| | | |
|---|---|---|
| Placebo | 3.3% | |
| HCTZ 12.5 mg | 6.2% | Certainly the potassium associated with |
| HCTZ 25 mg | 11.1% | HCTZ is apparent. |
| Valsartan 80 mg | 1.0% | |
| Valsartan 160 mg | 0.0% | |
| Valsartan 80/HCTZ 12.5 mg | 1.0% | |
| Valsartan 160/HCTZ 12.5 mg | 2.1% | |
| Valsartan 80/HCTZ 25 mg | 8.9% | Suggests a dose-related effect of valsartan. |
| Valsartan 160/HCTZ 25 mg | 4.4% | |

It is pretty clear that the usual effects of potassium loss associated with HCTZ are blunted by the combination product, and that valsartan alone is associated with potassium retention. The potassium loss related to HCTZ is , however, not completely prevented by the addition of valsartan even at a dose of 160 mg.

Black-White Responses to Valsartan. The table that follows represents the results of study 301 as raw change from baseline in sitting diastolic blood pressure, placebo subtracted in mm Hg. In () are the numbers of patients represented in the change. As can be seen, for every raw data comparison (White and Black columns), represented in the Black Minus White column, blacks had a drug effect greater than whites including valsartan alone. What can also be seen is that compared to their responses to HCTZ, blacks had less effect than whites when valsartan/HCTZ was administered. Of course, this ia a subgroup analysis that must be taken with a few grains (or more) of salt. It is what exists, and I do not think 14 supports any kind of labelling statement about black and white differences.

| Treatment Group | White | Black | Black Minus White | Valsartan Addition Black Minus White |
|---|---|---|---|---|
| Valsartan 80 | 4.5 (n=70) | 6.1 (n=15) | 1.6 | |
| Valsartan 160 | 6.0 (n=75) | 8.4 (n=12) | 2.4 | |
| HCTZ 12.65 | 3.0 (n=65) | 8.1 (n=22) | 5.1 | |
| HCTZ 25 | 4.6 (n=69) | 10.4 (n=11) | 5.8 | |
| Val/HCTZ, 80/12.5 | 7.6 (n=69) | 11.0 (n=12) | 3.4 | -1.1 |
| val/HCTZ, 80/25 | 10.6 (n=71) | 12.7 (n=9) | 2.1 | -3.7 |
| Val/HCTZ 160/12.5 | 9.9 (n=78) | 10.1 (n=10) | 0.2 | -4.9 |
| Val/HCTZ 160/25 | 12.0 (n=68) | 18.2 (n=15) | 6.2 | 0.2 |
| Total n | 419 | 91 | | |

**Summary**

I have marked on the attached draft labelling. It should be an approvable action.

cc:
Orig. NDA 20-818
HFD-110
HFD-110/KBongiovanni
HFD-110/RLipicky

FEB 4 1998

**Secondary Medical Review of NDA Application**

**NDA #:** 20-818
**Drug Name:** Valsartan/HCTZ
**Type of Document:** New Drug Application
**Date Received:** 4/01/97

**Sponsor:** Novartis
**Correspondence Date:** 3/28/97
**Date Completed:** 2/2/98
**Medical Reviewer:** Charles J. Ganley, M.D.

NDA Primary Reviewers

| Discipline | Reviewer |
|---|---|
| Chemistry | Stuart Zimmerman, Ph.D |
| Environmental Assessment | Florian Zielinski, Ph.D |
| Pharmacology | Estela Barry, M.S. |
| Biopharmacology | Emmanuel Fadiran, Ph.D |
| Statistics | Walid Nuri, Ph.D |
| Clinical Efficacy | Sughok Chun, M.D. |
| Clinical Safety | Akinwole Williams, M.D. |
| Scientific Investigation | None |

**Chemistry**

There are no outstanding Chemistry issues with the exception of a request from Dr. Zimmerman that the sponsor provide a stand alone stability protocol.

**Environmental Assessment**

The product can be manufactured, used and disposed without any expected adverse environmental effects.

**Pharmacology**

Chronic (6 month) oral dosing studies were performed in the rat at doses of 40, 131, and 394 mg/kg/day (valsartan/HCTZ ratio = 80/25). Mortality was prevalent in the majority of the animals exposed to the highest dose. Dose related increases were observed for blood urea, $Mg^{++}$, $K^{+}$, creatinine, ALT and AST. Reductions were noted for hemoglobin and hematocrit. Dose related increases in urine volume and electrolyte excretion were reported with therapy and returned to normal during a 28 day recovery period. Renal tubular basophilia was considered a treatment related phenomena on microscopic exam. Chronic oral dosing studies were also performed in the marmoset at doses of 40, 80, 158 and 315 mg/kg. Mortality was prevalent at the high dose. Changes in blood chemistries, hematology and urinary parameters that were observed in the rat study were also observed in the marmoset. Renal basophilia was also reported on microscopic examination. Loss of weight, vomiting, diarrhea and buccal ulcerations were observed. Kidney lesions included glomerular arterial hypertrophy, interstitial nephritis and tubular mineralization. Six of 40 marmosets had kidneys with focal tubular epithelial hyperplastic lesions (not observed in control group).

There were no carcinogenicity, genotoxicity, Segment I or Segment III studies performed with the combination. Segment II studies were performed in mouse, rat and rabbit. There was no definitive evidence of teratogenicity in any of the species. Cleft palate was observed in both the mouse and rat (p. 43, 49, 55) studies for the combination (rat, mouse) and HCTZ (mouse) groups. It was not observed in the rabbit study. None of the control group litters had cleft palate. This observation is noted only because cleft palate is apparently a rare finding in the rat. The relevance of this abnormality is not clear but it may be worthwhile for the sponsor to provide historical background rates for cleft palate in the mouse and rat.

**Biopharmacology**

The sponsor performed two bioequivalence studies that compare the fixed final market image tablet with the free combinations used in phase II clinical trials. Study 302 evaluated the bioequivalence of the valsartan 160 mg/HCTZ 12.5 mg tablet. Study 303 evaluated the bioequivalence of the valsartan 80 mg/HCTZ 12.5 mg tablet. The valsartan 80 mg/HCTZ 12.5 mg fixed final market image tablet was bioequivalent to the free combinations used in the phase II clinical trials. The valsartan 160 mg/HCTZ 12.5 mg fixed final market image tablet was not bioequivalent to the free combinations used in the phase II clinical trials because the $AUC_{\alpha}$ 90% Confidence Interval was 1.06 - 1.28. This interval exceeds the .8 - 1.25 interval generally accepted to declare products bioequivalent. For this drug product, the slight

deviation from the .8 - 1.25 interval is not clinically relevant and should not affect the approvability of this application.

The reviewer recommends the in vitro dissolution specification should be Q of at 30 minutes rather than Q of at 45 minutes as proposed by the sponsor.

**Patient Exposure**

The NDA included the results of two double-blind, placebo (protocol 301) or active (protocol 19) controlled trials in hypertensive patients where valsartan/HCTZ was one of the randomized therapies. In addition, there are two double-blind, active control, parallel dose trials (protocols 28 and 20) where open label HCTZ was added to those patients who did not respond to the original randomized therapy. Three open label studies (11E, 28E, 31E) exposed patients to long term therapy with valsartan or the combination of valsartan/HCTZ. Two studies (protocols 302 and 303) assessed the bioequivalence of the to be marketed formulation to the formulation used in clinical trials. Protocol 7 evaluated the pharmacokinetic drug interaction between HCTZ and valsartan. There was a single dose study (protocol 24)[1] of valsartan in patients volume depleted with triamterene and HCTZ. Table PE.1 lists the trials included in the submission.

**Table PE.1.** Studies Which Included Valsartan/HCTZ Therapy

| **Double Blind Controlled Trials** | | | | |
|---|---|---|---|---|
| Study | Design | Population | Treatments (mg) | N |
| 301 | r, mc, 8 wk db Rx, p, pc, factorial | • HTN | • placebo<br>• HCTZ 12.5 mg<br>• HCTZ 25 mg<br>• Valsartan 80 mg<br>• Valsartan 160 mg<br>• Valsartan/HCTZ 80/12.5<br>• Valsartan/HCTZ 80/25<br>• Valsartan/HCTZ 160/12.5<br>• Valsartan/HCTZ 160/25 | 94<br>100<br>100<br>99<br>99<br>96<br>92<br>97<br>94 |
| 19 | r, db, mc, ac, p | • HTN<br>• non-responders to valsartan | • Valsartan 80 mg<br>• Valsartan 160 mg<br>• Valsartan/HCTZ 80/12.5<br>• Valsartan/HCTZ 80/25 | 183<br>172<br>176<br>177 |
| **Active Control, Open Label HCTZ Added** | | | | |
| Study | Design | Population | Treatments (mg) | N |
| 28 | ac, db, p, 52 week Rx, dose titration, ol HCTZ 12.5 --> 25 mg added | • HTN<br>• ≥ 65 years of age | • Valsartan 40 --> 80 mg<br>• Lisinopril 2.5 --> 20 mg | 334<br>167 |
| 20 | r, db, p, ac, ol HCTZ 12.5 | • HTN | • valsartan 80 mg<br>• enalapril 20 mg | 94<br>95 |
| **Long Term Open Label** | | | | |
| Study | Design | Population | Treatments (mg) | $N_T/N_{VH}$ |
| 11E | ol, titration | • HTN | • valsartan +/- HCTZ | 399/185 |
| 28E | ol, titration | • HTN | • valsartan +/- HCTZ | 69/48 |
| 31E | ol, titration | • HTN | • valsartan +/- HCTZ | 376/197 |

r = randomized; mc = multi-center; db = double-blind; ac = active control; ol = open label; p = parallel; triam = triamterene; sd = single dose; Rx = treatment; wk = week; co = crossover;
$N_{VH}$ = total exposed to valsartan/HCTZ; $N_T$ = total randomized

[1] study 24 did not give the combination simultaneously

**Table PE.1.(con't.)** Studies Which Included Valsartan/HCTZ Therapy

| Other Studies | | | | |
|---|---|---|---|---|
| Study | Design | Population | Treatments (mg) | N |
| 7 | sd, r, co | • healthy males | • valsartan<br>• HCTZ | 12 |
| 302 | sd, r, 3 way co | • healthy males | • valsartan/HCTZ | 34 |
| 303 | sd, r, 3 way co | • healthy males | • valsartan/HCTZ | 35 |
| 24 | sd, db, 3 way co | • volume depleted with triam/HCTZ<br>• HTN | • valsartan 80 mg<br>• atenolol 50 mg<br>• lisinopril 10 mg | 35 |

r = randomized; mc = multi-center; db = double-blind; ac = active control; ol = open label; p = parallel; triam = triamterene; sd = single dose; Rx = treatment; wk = week; co = crossover;
$N_{VH}$ = total exposed to valsartan/HCTZ; $N_T$ = total randomized

In the controlled and uncontrolled trials, 1303 patients were exposed to valsartan/HCTZ. The majority of these patients received the combination therapy for less than 6 months. There were, however, 365 patients exposed for 6 - 12 months and 170 patients exposed for > one year. [section 5.1 and 5.1.3, Dr. Williams review]

**Efficacy**

There are two studies (protocol 301 and 19) that provide efficacy data. Study 301 is a randomized, double-blind, placebo controlled trial in patients with a mean sitting diastolic blood pressure ≥ 95 mmHg and ≤ 115 mmHg. The trial consisted of a 2 - 4 week placebo run-in followed by an eight week double-blind treatment group. Patients were randomized to placebo, valsartan, HCTZ or the combination of valsartan/HCTZ. The study randomized 871 patients.

Study 19 is a randomized, double-blind, parallel group trial in patients with a mean sitting diastolic blood pressure ≥ 95 mmHg and ≤ 120 mmHg. The trial consisted of a 2 week placebo period followed by a 4 week single blind treatment period during which patients received valsartan 80 mg. Patients not adequately controlled on valsartan 80 mg (sitting diastolic blood pressure ≥ 95 mmHg and ≤ 115 mmHg) were randomized to valsartan 80 mg, valsartan 160 mg, valsartan 80 mg/HCTZ 12.5 mg or valsartan 80 mg/HCTZ 25 mg for 8 weeks of double-blind treatment.

*Diastolic Blood Pressure*

In study 301, the primary measure of efficacy was the change from baseline in mean sitting diastolic blood pressure at endpoint. Tables E.1 and E.1a list the least square mean change and the change in siDBP using the raw data. Six patients did not have a post-randomization blood pressure measurement (1 placebo, 1 HCTZ 12.5 mg, 1 valsartan/HCTZ 80/12.5, 2 valsartan 160 mg, 1 valsartan/HCTZ 160/12.5) and are not included in the analysis.

**Table E.1.** Mean Change In siDBP (mmHg) From Baseline for Study 301. (least square mean)

| | placebo | Valsartan 80 mg | Valsartan 160 mg |
|---|---|---|---|
| placebo | - 4.1 | - 8.6 | - 9.4 |
| HCTZ 12.5 mg | - 7.2 | - 11.8 | - 13.5 |
| HCTZ 25 mg | - 9.3 | - 15.3 | -15.3 |

**Table E.1a.** Mean Change In siDBP (mmHg) From Baseline for Study 301. (mean raw data)

| | placebo | Valsartan 80 mg | Valsartan 160 mg |
|---|---|---|---|
| placebo | - 4.0 (7.7) | - 8.3 (8.1) | - 10.4 (9.1) |
| HCTZ 12.5 mg | - 7.6 (7.9) | - 12.1 (7.9) | - 13.5 (8.4) |
| HCTZ 25 mg | - 9.1 (8.2) | - 14.8 (7.8) | - 16.1 (9.4) |

Dr. Nuri performed an analysis[2] to determine whether one of the four combinations is superior to its individual components. Using this test, there was at least one combination that was superior ($p < 0.0001$) to its components. Further testing by Dr. Nuri (page 3 of his review) utilizing a Bonferoni

[2] based on Hung. Chi, Lipicky (Biometrics 1993)

approach and Hochberg MC procedure to adjust for multiple comparisons, all combinations were superior to placebo and its individual components. Further analysis (page 5 Dr. Nuri's review) fitting the data to a Emax response surface model suggested that the maximum dose of the combination at which Emax is achieved was beyond the doses studied.

In study 19, the primary measure of efficacy was the change from baseline in trough mean sitting diastolic blood pressure at endpoint. Table E.2 lists the mean change from baseline in siDBP at endpoint. This study shows that the addition of HCTZ (12.5 mg or 25 mg) to valsartan 80 mg causes a significant reduction in siDBP compared to valsartan 80 mg.

**Table E.2.** Mean Sitting DBP (mmHg ) Measurements and Change from Baseline at Endpoint. [NDA #20-665, vol. 1.159, p. 181]

| | Valsartan 80 mg | Valsartan 160 mg | Valsartan 80 mg / HCTZ 12.5 mg | Valsartan 80 mg / HCTZ 25 mg |
|---|---|---|---|---|
| N* | 179 | 171 | 176 | 176 |
| Baseline** | 100.21 (4.94) | 99.83 (4.5) | 99.89 (5.14) | 100.6 (5.13) |
| Endpoint | 94.95 (9.17) | 94.12 (8.12) | 92.04 (9.33) | 90.22 (9.69) |
| Change | - 5.26 (7.72) | - 5.71 (7.19) | - 7.85 (7.96) | - 10.38 (8.04) |

* the number of subjects with at least one post-baseline BP measurement; ** visit 3 measurement

*Responders*

The proportion of patients achieving a successful response[3] in study 301 is listed in table E.3. If the Bonferoni and Hochberg procedures are utilized to adjust for multiple comparisons, the valsartan/HCTZ 80/12.5 combination is not significantly different from the individual components.[4] The other combinations were significantly different compared to their individual components.

**Table E.3.** Percentage of Responders in Study 301

| | placebo | Valsartan 80 mg | Valsartan 160 mg |
|---|---|---|---|
| placebo | 29% | 54% | 59% |
| HCTZ 12.5 mg | 41% | 64% | 76% |
| HCTZ 25 mg | 54% | 81% | 81% |

*Subgroups*

In study 301, the mean change in siDBP based on age, gender and race are listed in table E.4., E.4a. and E.4b respectively. There are more males, caucasians and patients < 65 years. For all treatment groups except the valsartan 160/HCTZ 25 group, the effect in the ≥ 65 year age group was greater than the < 65 year age group. Males were generally less responsive than females (table E.5.a). Black patients were very responsive to HCTZ and experienced less of an additive effect with valsartan 80 mg.

**Table E.4.** Placebo Subtracted Change in siDBP (mmHg) Based on Age Group for Study 301.

| | Age | placebo | | Valsartan 80 mg | | Valsartan 160 mg | |
|---|---|---|---|---|---|---|---|
| | | N | Δ siDBP | N | Δ siDBP | N | Δ siDBP |
| Placebo | < 65 | 85 | - | 86 | - 3.9 | 82 | - 6.2 |
| | ≥ 65 | 8 | - | 13 | - 7.5 | 15 | - 7.7 |
| HCTZ 12.5 mg | < 65 | 82 | - 3.0 | 82 | - 8.2 | 81 | - 9.1 |
| | ≥ 65 | 17 | - 6.3 | 14 | - 7.6 | 15 | - 11.4 |
| HCTZ 25 mg | < 65 | 87 | - 4.7 | 80 | - 10.5 | 77 | - 13.2 |
| | ≥ 65 | 13 | - 7.9 | 11 | - 13.1 | 17 | - 7.3 |

[3] siDBP < 90 mm Hg or ≥ 10 mmHg decrease compared to baseline

[4] using the calculated p values from page 17 of Dr. Chun's review and the multiple comparison procedures outlined in Dr. Nuri's review.

**Table E.4a.** Placebo Subtracted Change in siDBP (mmHg) Based on Gender for Study 301.

| | Gender | placebo | | Valsartan 80 mg | | Valsartan 160 mg | |
|---|---|---|---|---|---|---|---|
| | | N | Δ siDBP | N | Δ siDBP | N | Δ siDBP |
| Placebo | F | 35 | - | 36 | - 6.8 | 37 | - 9.6 |
| | M | 58 | - | 63 | - 2.9 | 60 | - 4.4 |
| HCTZ 12.5 mg | F | 42 | - 7.8 | 38 | - 8.9 | 44 | - 13.5 |
| | M | 57 | -.7 | 58 | - 7.6 | 47 | - 8.9 |
| HCTZ 25 mg | F | 45 | - 7.9 | 38 | - 12.3 | 43 | - 15.7 |
| | M | 55 | - 3.1 | 58 | - 7.8 | 51 | - 9.5 |

**Table E.4b.** Placebo Subtracted Change in siDBP (mmHg) Based on Race for Study 301.

| | Race | placebo | | Valsartan 80 mg | | Valsartan 160 mg | |
|---|---|---|---|---|---|---|---|
| | | N | Δ siDBP | N | Δ siDBP | N | Δ siDBP |
| Placebo | White | 70 | | 75 | -4.5 | 75 | -6.0 |
| | Black | 13 | | 15 | -6.1 | 12 | -8.4 |
| | Other | 10 | | 9 | -1.0 | 10 | -6.3 |
| HCTZ 12.5 mg | White | 65 | -3.0 | 69 | -7.6 | 78 | -9.8 |
| | Black | 22 | -8.1 | 12 | -11.0 | 10 | -10.1 |
| | Other | 12 | -1.5 | 15 | -7.2 | 8 | -3.8 |
| HCTZ 25 mg | White | 77 | -4.6 | 71 | -10.9 | 68 | -12.0 |
| | Black | 11 | -10.4 | 9 | -12.7 | 15 | -18.2 |
| | Other | 12 | -2.4 | 11 | 19.4 | 11 | -5.5 |

The subgroup analysis for study 19 (table E.5.) yields similar results as the analysis for study 301.

**Table E.5.** Mean Change in siDBP (mmHg) in Study 19 by Subgroup.

| Subgroup | Valsartan 80 mg | | Valsartan 160 mg | | Valsartan 80 mg/ HCTZ 12.5 mg | | Valsartan 80 mg/ HCTZ 25 mg | |
|---|---|---|---|---|---|---|---|---|
| | N | Δ siDBP | N | Δ siDBP | N | Δ siDBP | N | Δ siDBP |
| Female | 66 | -5.4 | 62 | -7.3 | 59 | -8.0 | 53 | -12.6 |
| Male | 113 | -5.2 | 109 | -4.8 | 117 | -7.8 | 123 | -9.4 |
| | | | | | | | | |
| < 65 years | 152 | -5.2 | 145 | -5.5 | 151 | -7.6 | 141 | -9.7 |
| ≥ 65 years | 27 | -5.5 | 26 | -6.9 | 25 | -9.6 | 35 | -13.2 |
| | | | | | | | | |
| White | 127 | -5.6 | 123 | -6.3 | 121 | -8.1 | 125 | -11.1 |
| Black | 28 | -4.5 | 23 | -2.2 | 29 | -8.6 | 25 | -9.1 |
| Other | 24 | -4.5 | 25 | -6.0 | 26 | -5.7 | 26 | -8.1 |

*Systolic Blood Pressure*

The least square mean change in siSBP for study 301 are listed in Table E.6. As with diastolic blood pressure, the combinations are superior to their individual components.

**Table E.6.** Mean Change In siSBP (mmHg) From Baseline (raw means) for Study 301.

| | placebo | Valsartan 80 mg | Valsartan 160 mg |
|---|---|---|---|
| placebo | - 1.7 (13.0) | - 8.2 (14.3) | - 12.6 (16.6) |
| HCTZ 12.5 mg | - 7.6 (14.3) | - 16.8 (13.3) | - 18.7 (12.6) |
| HCTZ 25 mg | - 12.1 (13.6) | - 20.4 (12.7) | - 23.2 (14.5) |

In study 19, the addition of HCTZ to valsartan 80 mg causes a decrease in siSBP (table E.7).

**Table E.7.** Mean Sitting SBP (mmHg) Measurements and Change from Baseline at Endpoint for Study 19. [NDA #20-665, vol. 1.159, p. 183]

| | Valsartan 80 mg | Valsartan 160 mg | Valsartan 80 mg / HCTZ 12.5 mg | Valsartan 80 mg / HCTZ 25 mg |
|---|---|---|---|---|
| N* | 179 | 171 | 176 | 176 |
| Baseline** | 150.15 (15.3) | 149.27 (15.3) | 149.63 (14.1) | 152.41 (15.2) |
| Endpoint | 146.34 (16.2) | 143.35 (16.9) | 140.31 (16.9) | 136.68 (16.6) |
| Change | - 3.81 (11.6) | - 5.92 (11.3) | - 9.32 (12.7) | - 15.74 (15.3) |

* the number of subjects with at least one post-baseline BP measurement; ** visit 3 measurement

**Safety**

*Deaths*

Three patients died while receiving valsartan/HCTZ in open label studies. Patient 509 in protocol 11E1 died from atherosclerotic heart disease. Patient 1031 in protocol 28E died from complications after gall bladder surgery. Patient 62 in protocol 28 experienced a sudden death. There were eight deaths in patients receiving valsartan monotherapy. All were on valsartan 80 mg or less. None of the deaths could be directly attributed to valsartan or HCTZ therapy.

*Adverse Events*

The overall safety profile of valsartan/HCTZ is rather unremarkable. Serious adverse events were reported by approximately 5% of patients exposed to valsartan/HCTZ. The majority of these are from the open label uncontrolled trials. Most cannot be attributed to valsartan/HCTZ but there are cases of syncope, hypokalemia, hyponatremia and volume depletion where valsartan/HCTZ was probably a contributing factor. These cases are rare but they are in the database and may be more of a problem when a more heterogeneous population is exposed to therapy. Angioedema was not reported but there are reports (e.g. face edema, eye edema) that may reflect a similar process.

There were no significant differences in the overall incidence of adverse events in protocols 19 and 301 between valsartan/HCTZ treated patients and others. Headache, dizziness and fatigue are the most commonly reported. There appears to be a greater incidence of dizziness in valsartan/HCTZ (6.3% - 16%) verses valsartan monotherapy patients (2.2% - 3.0%). This difference in dizziness probably reflects the design of the trials (parallel dose groups versus dose titration) and may not be as large a problem in clinical practice. There do not appear to be any age, race[5] or sex related differences in the incidence of adverse events. The majority of adverse events are considered mild in intensity. Headache was more likely to be severe in the placebo patients (3.2%) compared to the valsartan/HCTZ (1.2%) group.

Dizziness was the most common adverse event leading to premature discontinuation (0.6%) in the valsartan/HCTZ patients in the controlled and uncontrolled trials.

*Laboratory*

There is a slight decrease in the mean hemoglobin and hematocrit compared to placebo similar to that observed with other AII antagonists and ACE inhibitors. The decline in mean potassium observed with HCTZ is somewhat but not completely ameliorated by the addition of valsartan. This observation is also applicable to shift tables[6] that compare the baseline and terminal laboratory values. Hypokalemia was reported in some patients receiving valsartan/HCTZ but the lowest values were generally between 3.0 - 3.5 mEq/L. As with potassium, the decline in sodium caused by HCTZ alone is incompletely ameliorated by the addition of valsartan. Valsartan had no effect on the increase in uric acid levels observed with HCTZ alone. Table S.1 shows the mean change in various laboratory parameters in the controlled trials.

---

[5] there was limited exposure in patients > 65 and black patients

[6] low or normal lab ---> high lab; high or normal lab ---> low lab

**Table S.1.** Mean Change in Various Lab Parameters in Controlled trials (Baseline to Terminal Measure).

| Lab Parameter | Valsartan/HCTZ | Valsartan | HCTZ | Placebo |
|---|---|---|---|---|
| Potassium (mEq/dl) | -.15 | .03 | -.23 | -.03 |
| Sodium (mEq/dl) | -.2 | .08 | -.42 | .26 |
| Hemoglobin | -.15 | -.14 | .03 | .08 |
| Hematocrit | -.69 | -.66 | .16 | .30 |
| Uric Acid | .61 | -.05 | .56 | .09 |

**Conclusions**

The combination of valsartan and HCTZ at doses of 80/12.5, 80/25, 160/12.5 and 160/25 are superior to the individual components for lowering diastolic blood pressure. The combinations appear to be safe. Valsartan doses greater than 160 mg have not been studied in combination with HCTZ.

The sponsor should submit historical background rates of cleft palate in the rat and mouse in order to provide additional perspective regarding the relevance of this abnormality with valsartan/HCTZ in the Segment II studies.

**Labeling**

- The sponsor did not conduct a food effect study with the combination. A food effect study with valsartan monotherapy suggested a decrease in AUC (41%) and Cmax (53%) with food. A food effect pharmacodynamic study suggested there was no appreciable effect of food on the blood pressure effect with valsartan monotherapy. Thus, unless there is an appreciable food effect with HCTZ, there is no reason that the combination should not be given with or without food.
- The dosage and administration section should allow for the use of doses as high as valsartan 160 mg/HCTZ 25 mg (two tablets of valsartan 80 mg/HCTZ 12.5 mg tablets).
- Valsartan 80 mg does not completely ameliorate the potassium lowering effect of 12.5 mg of HCTZ.

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / Project Manager / C. Ganley /F. Williams/ S. Chun
HFD-710/ W. Nuri
HFD-860/ E. Fadiran
HFD-810 / Zimmerman / Zielinski

Consult #791(HFD-110)

DIOVAN HCT valsarten and hydrochlorthiazide 80/12.5 mg and 160/12.5mg

DIOVAN is an already approved product and was not considered by the LNC. The letters HCT are discouraged however, since they are commonly used to designate not only hydrochlorthiazide but hydrocortisone and hematocrit.

The Committee finds the proposed proprietary name unacceptable.

6/23/97, Chair
CDER Labeling and Nomenclature Committee

REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: April 3, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Diovan HCT NDA/ANDA 20-818

Trademark status: Yes No Pending X

Company Name: Novartis Pharmaceuticals

Other proprietary names by the same firm for companion products:
Diovan (valsartan) L&N committee approved the name.
Established name including dosage form and strength:
Valsartan & Hydrochlorothiazide 80 /12.5 & 160/12.5 mg

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Treatment of hypertension.

Comments from the submitter: (concerns, observations, etc.)

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.96

**PATENT INFORMATION**
**DIOVAN HCT™**
VALSARTAN / HYDROCHLOROTHIAZIDE TABLETS
21 CFR 314.50 (h)

NDA 20-818

| | |
|---|---|
| Patent Number: | U.S. 5,399,578 |
| Patent Expiration Date: | March 21, 2012 |
| Type of Patent: | Active Ingredient, Composition/Formulation, Method of Use |
| Name of Patent Owner: | CIBA-GEIGY Corporation |
| Indication: | Hypertension |
| Strengths: | 80 mg valsartan / 12.5 mg hydrochlorothiazide & 160 mg valsartan / 12.5 mg hydrochlorothiazide |

The undersigned declares that the above stated United States Patent Number covers the composition, formulation and/or method of use of Diovan HCT (valsartan / hydrochlorothiazide). This product is the subject of this application for which approval is being sought.

Signed _____ Date 3/20/97

Nancy A. Price
Associate Director
Drug Regulatory Affairs

zpatent.doc

FEB 20 1998

**EXCLUSIVITY SUMMARY for NDA #** 20-818 **SUPPL #** _____

**Trade Name** Diovan HCT Tablets **Generic Name** valsartan / HCTZ
**Applicant Name** Novartis **HFD-** 110

**Approval Date** 2/20/98

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.**

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 301

Investigation #2, Study # 19

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 301 YES /___/ NO /✓/

Investigation #2 19 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 301 YES /___/ NO /✓/

Investigation #2 19 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 301

Investigation #2, Study # 19

Investigation #__, Study # _____.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

| Investigation #2 | |
|---|---|
| YES /___/ Explain _____ | NO /___/ Explain _____ |
| _____ | _____ |
| _____ | _____ |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

_____ 2-18-98

Signature Date

Title: Regulatory Health Project Manager

_____ 2/20/98

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

K.B
MAR 6 1998

**PEDIATRIC PAGE**

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

(NDA)/BLA # 20-818 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: Diovan HCT (valsartan/hydrochlorothiazide) Tablets Action: (AP) AE NA

Applicant Novartis Therapeutic Class 45

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application for the treatment of hypertension

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ___Yes (Continue with questions) ___No (Sign and return the form)

**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See comments on second page.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

**ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER?** ___ Yes ___ No
**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from CHARLES GANLEY (e.g., medical view, medical officer, team leader)

Medical Officer. 3/6/98
Signature of Preparer and Title Date

cc: Orig (NDA)/BLA # 20-818
HFD-110 /Div File
NDA/BLA Action Package/KBongiovanni
HFD-006/ KRoberts

(revised 10/20/97)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)**

Pediatric Studies are not needed because the drug is indicated in the hypertension which has a low incidence in the pediatric population.

V

Ciba

Novartis Pharmaceuticals Corporation

**New Drug Application for**

**Diovan HCT™**

**(Valsartan / Hydrochlorothiazide)**

## CERTIFICATION STATEMENT (21 U.S.C. 335a)

Novartis Pharmaceuticals Corporation hereby certifies that, to the best of its knowledge, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this application.

Signed Nancy A. Price Date 3/18/97

Nancy A. Price
Associate Director
Drug Regulatory Affairs

zndaastmt.doc

Ciba

Novartis Pharmaceuticals Corporation

**New Drug Application for**

**Diovan HCT™**

**(Valsartan / Hydrochlorothiazide)**

## FIELD COPY CERTIFICATION STATEMENT (21 CFR 314.50)

Novartis Pharmaceuticals Corporation hereby certifies that the field copy of this application is a true copy of the technical documentation contained in the archival and review copies of the same application. The field copy has been provided to the FDA New Jersey District office in North Brunswick, NJ.

Signed Nancy A. Price Date 3/18/97

Nancy A. Price
Associate Director
Drug Regulatory Affairs

zndestmt.doc

Ciba

Novartis Pharmaceuticals Corporation

**New Drug Application for**

**Diovan HCT™**

**(Valsartan / Hydrochlorothiazide)**

## PENTIUM PROCESSOR CERTIFICATION STATEMENT

Novartis Pharmaceuticals Corporation hereby certifies that no calculations were performed using a pentium processor in connection with this application.

Signed Nancy A. Price Date 3/18/97

Nancy A. Price
Associate Director
Drug Regulatory Affairs

zndaxtrvt.doc

RHPM NDA Overview
February 5, 1998

**NDA 20-818** Diovan HCT (valsartan/hydrochlorothiazide)
80/12.5 and 160/12.5 mg Tablets

**Sponsor:** Novartis Pharmaceuticals Corporation

**Classification:** 4S

**Date of Application:** March 28, 1997
**Date of Receipt:** March 31, 1997
**User Fee Goal Date:** March 31, 1998

**Background**: Novartis has submitted this NDA for the combination product valsartan/HCTZ for the treatment of hypertension. Valsartan monotherapy was approved for the treatment of hypertension under NDA 20-665 on December 23, 1996. Studies for the combination were performed under

Meetings
May 5, 1997: Filing meeting.

January 12, 1995: Meeting to discuss clinical development plan for the combination; Dr. Lipicky encouraged the firm to study a broader range of doses.

January 13, 1994: End-of-Phase II Meeting for valsartan. meeting included a discussion of a factorial trial for the combination product.

Letters/Telecons During Review:
January 13, 1998: Letter containing Medical, Biopharm, Pharm, and Chem reviews

December 5, 1997: Telecon to discuss dissolution specifications and sampling times.

November 6, 1997: Letter containing EFadiran 10-30-97 biopharm review

**STATUS:**

Medical Review
Medical Reviewers: Sughok Chun, M.D. (efficacy)
Akinwole Williams, M.D. (safety)
Labeling: see Dr. Chun's 11-5-97 review and Dr. Williams'1-30-98 review for labeling recommendations. (These recommendations were discussed on 2-2-98 and changes have been incorporated into the revised draft labeling.)
Conclusion: Chun: approvable
Williams: approvable

Biopharmaceutics Review:
Reviewer: Emmanuel Fadiran, Ph.D.
Labeling: see recommendations on page 3 of10-30-97 review. (These recommendations were discussed on 2-2-98 and changes have been incorporated into the revised draft labeling.)
Conclusion: approvable

Statistics (clinical)
Reviewer: Walid Nuri, Ph.D.
Labeling: none
Conclusion: effective combination

Chemistry:
Reviewer: Stuart Zimmerman, Ph.D.
Carton & container labeling:
Labeling: acceptable
cGMP Inspections: Acceptable September 19, 1997
Methods validation: not complete
Conclusion: approvable; on 12-19-97 Novartis agreed to provide a stand-alone stability protocol by telephone; they will submit a letter with the details of their commitment.

Environmental Assessment:
Reviewer: Florian Zielinski, Ph.D.
FONSI approved June 30, 1997.

Pharmacology-
Reviewer: Estela Barry, M.S.
Labeling: see recommended changes on page 82.
Conclusion: Approvable. The firm should be encouraged to conduct the genotoxicity mouse lymphoma tk assay of the drug combination as well as of the HCTZ.

Statistics (preclin): Not needed.

Safety Update: In August 1, 1997 submission, firm states that there were no trials ongoing at time of NDA submission and none have been initiated, so there are no further data available.

Patent info: included in package

Debarment Certification: included in package

DSI Inspections- Antoine El Hage, Ph.D. : Were to be done only if Drs. Williams, Chun, and Nuri requested study-oriented inspections; none requested/none performed.

CDER Labeling & Nomemclature Committee: "DIOVAN is an already approved product and was not considered by the LNC. The letters HCT are discouraged however, since they are commonly used to designate not only hydrochlorothiazide but hydrocortisone and hematocrit. The Committee finds the proposed proprietary name unacceptable." June 23, 1997.
The chemists believe the name is acceptable; see Chem review 1, pages 2 and 11.

Kathleen F. Bongiovanni

2-5-98

cc:
NDA 20-818
HFD-110
HFD-111/SBenton
HFD-111/KBongiovanni
kb/2/5/98.

RHPM Review of Labeling MAR 6 1998

NDA: 20-818 Diovan HCT (valsartan/hydrochlorothiazide)
80/12.5 and 160/12.5 Tablets

Date of submission: February 24, 1998

Date of receipt: February 25, 1998

Applicant: Novartis

**Background**: On February 20, 1998, Dr. Lipicky signed an approvable letter for NDA 20-818, requesting final printed labeling identical to the enclosed marked-up draft labeling.

**Review**: I have reviewed the submitted final printed labeling. The language is identical to the language in the draft labeling included with the approvable letter. In the marked-up draft labeling, we requested that the firm delete "USP" from the labeling. The labeling still includes "USP" in a header on the top of the reverse side. In a telephone conversation with Ms. Nancy Price on February 25, 1998, they agreed to delete this at the time of their next printing.

**Recommendation**: I will prepare an approval letter for this NDA for Dr. Lipicky's signature.

2-27-98

Kathleen F. Bongiovanni

cc: NDA 20-818
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/3/3/98.