

21-283

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-283**

**Trade Name:** Diovan Tablets  
80-, 160-, and 320 mg

**Generic Name:** Valsartan

**Sponsor:** Novartis Pharmaceuticals, Corporation

**Approval Date:** July 8, 2001

**Subject:** For the treatment of hypertension

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-283**

**Approval Letter**



NDA 21-283

Novartis Pharmaceuticals Corporation  
Attention: Ms. Nancy A. Price  
59 Route 10  
East Hanover, NJ 07936-1080

JUL 8 2001

Dear Ms. Price:

Please refer to your new drug application (NDA) dated August 7, 2000, received August 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 80, 160, and 320 mg Tablets.

We acknowledge receipt of your submissions dated June 11, 13, 18, 19, and July 9, 2001. Your submission of June 18, 2001 constituted a complete response to our June 8, 2001 approvable letter.

This new drug application provides for the use of Diovan (valsartan) 80, 160, and 320 mg Tablets for the treatment of hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels included in your June 18, 2001 submission). Accordingly, the application is approved effective on the date of this letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please note that as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are deferring submission of your pediatric studies until December 19, 2004. We note that you have submitted the status of your pediatric drug development plans in your submission dated June 11, 2001.

We note that you have agreed in your July 17, 2001 telephone conversation with Dr. Quynh Nguyen to remove the phrase "30 tablets, 90 tablets or" from the second sentence under the **HOW SUPPLIED** section of the package insert at the next printing. This should be reported in the annual report.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-283

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Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager  
(301) 594-5311

Sincerely,

*{See appended electronic signature page}*

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-283**

**Approvable Letter**

- Method of Preparation and Flow Sheet of Manufacture documents for Diovan 80 mg, 160 mg and 320 mg film-coated tablets reflecting the revised % in-process limit for LOD.

Please note that as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are deferring the pediatric study requirement for this action on this application until December 19, 2004.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager  
(301) 594-5311

Sincerely,

/S/

6/8/01

{See appended electronic signature page}

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-283**

**Final Printed Labeling**



89004205

NOVARTIS

T2001-47  
89004205**Diovan®**  
valsartan

Tablets

Rx only

## Prescribing Information

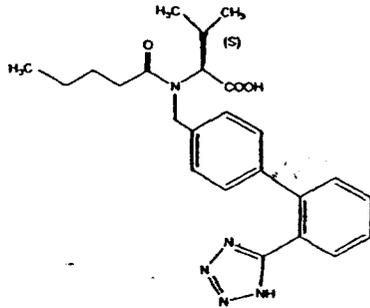
**USE IN PREGNANCY**

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

**DESCRIPTION**

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT<sub>1</sub> receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*[(2'-{(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-L-valine. Its empirical formula is C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as tablets for oral administration, containing 80 mg, 160 mg or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, croscopovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

**CLINICAL PHARMACOLOGY****Mechanism of Action**

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT<sub>2</sub> receptor found in many tissues, but AT<sub>2</sub> is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT<sub>1</sub> receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

**Pharmacokinetics**

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Diovan is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C<sub>max</sub>) by about 50%. AUC and C<sub>max</sub> values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

**Metabolism and Elimination**

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.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

**Distribution**

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

**Special Populations**

**Pediatric:** The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

**Geriatric:** Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

**Gender:** Pharmacokinetics of valsartan does not differ significantly between males and females.

**Renal Insufficiency:** There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).  
**Hepatic Insufficiency:** On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

**Pharmacodynamics and Clinical Effects**

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Diovan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily

regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

## INDICATIONS AND USAGE

Diovan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

## CONTRAINDICATIONS

Diovan is contraindicated in patients who are hypersensitive to any component of this product.

## WARNINGS

### Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during

the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

### Hypotension in Volume- and/or Salt-Depleted Patients

Excessive reduction of blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

## PRECAUTIONS

### General

**Impaired Hepatic Function:** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

### Information for Patients

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Diovan®**  
valsartan

**Drug Interactions**

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

**CYP 450 Interactions:** The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

**Pregnancy Categories C (first trimester) and D (second and third trimesters)**

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

**Nursing Mothers**

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

In the controlled clinical trials of valsartan, 1214 (36.2%) of patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

**ADVERSE REACTIONS**

Diovan has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-

inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p < 0.001).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

**Body as a Whole:** Allergic reaction and asthenia

**Cardiovascular:** Palpitations

**Dermatologic:** Pruritus and rash

**Digestive:** Constipation, dry mouth, dyspepsia, and flatulence

**Musculoskeletal:** Back pain, muscle cramps, and myalgia

**Neurologic and Psychiatric:** Anxiety, insomnia, paresthesia, and somnolence

**Respiratory:** Dyspnea

**Special Senses:** Vertigo

**Urogenital:** Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

**Post-Marketing Experience**

The following additional adverse reactions have been reported in post-marketing experience:

**Hypersensitivity:** There are rare reports of angioedema;

**Digestive:** Elevated liver enzymes and very rare reports of hepatitis;

**Renal:** Impaired renal function;

**Clinical Laboratory Tests:** Hyperkalemia;

**Dermatologic:** Alopecia.

**Clinical Laboratory Test Findings**

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

**Creatinine:** Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials.

**Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

**Liver function tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

**Neutropenia:** Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

**Serum Potassium:** Greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients.

**OVERDOSAGE**

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m<sup>2</sup> basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

**DOSAGE AND ADMINISTRATION**

The recommended starting dose of Diovan is 80 mg once daily when used as

monotherapy in patients who are not volume-depleted. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required, the dosage may be increased to 160 mg or 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

#### HOW SUPPLIED

Diovan is available as tablets containing valsartan 80 mg, 160 mg or 320 mg. All strengths are packaged in bottles of 30 tablets, 90 tablets or 100 tablets and unit dose blister packages. Tablets are debossed as follows:

80 mg Tablet - Pale red, almond-shaped with bevelled edges, debossed with DV on one side and NVR on the other.

Bottles of 100 .....NDC 0078-0358-05  
Unit Dose (blister pack) .....NDC 0078-0358-06  
Box of 100 (strips of 10)

160 mg Tablet - Grey-orange, almond-shaped with bevelled edges, debossed with DX on one side and NVR on the other.

Bottles of 100 .....NDC 0078-0359-05  
Unit Dose (blister pack) .....NDC 0078-0359-06  
Box of 100 (strips of 10)

320 mg Tablet - Dark greyish violet, almond-shaped with bevelled edges, debossed with DXL on one side and NVR on the other.

Bottles of 100 .....NDC 0078-0360-05  
Unit Dose (blister pack) .....NDC 0078-0360-06  
Box of 100 (strips of 10)

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

[See USP controlled room temperature.]

Protect from moisture.

Dispense in light container (USP).

REV: JUNE 2001

Printed in U.S.A.

T2001-47  
89004205

 NOVARTIS

Distributed by  
Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-283**

**Chemistry Review(s)**

## Memorandum

**To:** NDA 21-283 File

**From CMC Reviewer:** Stuart Zimmerman, HFD-110 (Clinical)/HFD-810

**Memorandum Date:** July 12, 2001

**Submission Date:** July 9, 2001

**Drug Product Name:** Diovan Tablets (valsartan)

**Subject:** Review of pending CMC issues addressed in applicant's submission dated July 9, 2001

**Background Status, CMC Evaluative Purpose and Conclusion:** This response seeks to resolve outstanding CMC control issues as noted in the FDA approvable letter dated June 8, 2001

- 1. Monograph Control Document for Valsartan Drug Substance:** The Attachment 2 indicates that a "Ciba Monograph" is provided as a final document (valid date: 25-June-2001) that incorporates the tighter control limits as expected. These subject changes are submitted apart from the completely revised monograph with the understanding that such fully documented specifications will be submitted to FDA in the 2001 Annual Report for Diovan Capsules (NDA 20-665) since this is where all the drug substance documentation is located by reference.
- 2. Drug Product Specification Revisions:** The requested specification changes for the 80 mg, 160 mg and 320 mg tablets are appropriately revised apart from the totally revised testing monograph, Monograph (DP-104\_R). It is noted that the applicant has elected to provide for the dissolution specifications so it only apply to levels 1 and 2 in the USP 24 <721> p. 1943) Acceptance Table for dissolution testing (This is a stricter provision than normal). This provision for a reduced kind of testing is an exception and is considered to be acceptable as noted by Dr. Patrick Marroum (HFD-110 biopharmaceutics team leader) on an informal consult basis.
- 3. Drug Product Method of Preparation:** The requested LOD limit of NMT % is provided for under *In-process Controls* and a revised drug product is revised that shows that the testing will be conducted.

**Conclusions:** There are no further pending CMC issues. The NDA may be approved from a CMC perspective.

/s/

Stuart Zimmerman

File: Memo(7-12-01)N21-283



NDA 21-283

Novartis Pharmaceuticals Corporation  
Attention: Ms. Nancy A. Price  
59 Route 10  
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your new drug application (NDA) dated August 7, 2000, received August 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 80, 160, and 320 mg Tablets.

We acknowledge receipt of your submissions dated October 10 and December 19, 2000, and January 22, April 3, May 3, 23 and 30 (two), 2001.

This new drug application provides for the use of Diovan (valsartan) 80, 160, and 320 mg Tablets for the treatment of hypertension.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the agreed upon submitted draft labeling. Please provide in the FPL submission the actual carton and container labeling for Diovan 160 mg tablet samples.

We remind you that the dissolution specification for Diovan (valsartan) 80, 160, and 320 mg Tablets is Q= % at 30 minutes.

In addition, the release and stability specifications for impurities for both the drug substance and drug product are as follows:

Valsartan Drug Substance	Drug Product (Both release and shelf-life)
≤ 1.0%	≤ 1.0%
≤ 0.5%	≤ 0.5%
Total related substances excluding ≤ 1.0%	Total related substances excluding ≤ 1.0%

Please provide the following revised documents by July 15, 2001 as general correspondence:

- Novartis Monograph control documents for drug substance and drug product (release and shelf-life) specifications mentioned above.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #21-283 DATE REVIEWED: 5/31/01

REVIEW #: 3 REVIEWER: Stuart Zimmerman

<u>SUBMISSION TYPE</u>	<u>DOCUMENT</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendments (CMC)	May 30, 2001	June 1, 2001	June 1, 2001
Amendment (labeling)	"	May 30, 2001	"

NAME & ADDRESS OF APPLICANT:

DRUG PRODUCT NAME

Proprietary: Diovan Tablets  
Established: Valsartan  
Code Name/#: CGP 48 933

CHEM. TYPE/THER. CLASS: 3S

PHARMACOL. CATEGORY/INDICATION: Orally active angiotensin II antagonist

DOSAGE FORM: Tablet

STRENGTHS: 80 mg, 160 mg and 320 mg

ROUTE OF ADMINISTRATION: Oral

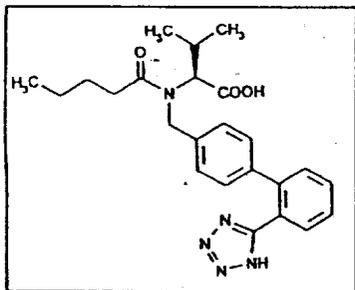
Rx/OTC: Rx Yes

SPECIAL PRODUCTS: No X

CHEMICAL NAME, STRUCTURAL FORMULA : (S)-N-Valeryl-N-{{2'-(1H-tetrazole-5yl)-biphenyl-4-yl]-methyl}-valine

Mol. Wt. = 435.5

Mol Formula : C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>



SUPPORTING DOCUMENTS:

- NDA 20-665 for Diovan Capsules
- NDA 20-818 for Diovan/HCT Tablets
- **DMFs (Type II):** The only Type II DMF involved is the one provided by the drug substance for which DMF is referenced in the NDA 20-665 for the Diovan Capsules. All the other synthetic operations are reported in the NDA 20-665 since facilities are involved.

**DMFs Involved:** This listing deals certain primary DMFs involved (e.g., for the ) and cross reference to previously approved NDA 20-665 and 20-818 utilizations.

DMF #	TYPE	HOLDER	ITEM REF.	STATUS CODE <sup>1</sup>	STATUS	DATE REVIEW	REVIEWER (NAME)
	III			1	OK	NA	NA
	III			1, 5	OK	NA	NA
	III			1	OK	NA	NA
	III			1	OK	NA	NA
	III			2	OK	NA	NA
	III			2, 3	OK	NA	NA
	III			1	OK	NA	NA
	III			3	OK	NA	NA
	III			6	OK	8/2/99	HFD-120 Christdoulos
	III			3	OK		N/A
	III			4	OK		NA
	III			4	OK		NA
	IV			5	OK	5/21/01 (3)	S Zimmerman

**Table Notes:** Extended evaluative comments are provided in the container-closure section of this review.

\*

is the current name for this DMF

\*\* The firm was called : for NDA 20-818 – name change involved.

**Note #1:** Refer to Chemistry Review #1 for NDA 20-818 (p. 7) for reference to previously approved status.

**Note #2:** Refer to Chemistry Review #1 for NDA 20-665 for reference to previously approved status.

**Note #3:** Issue resolved concerning equivalency of utilized

**Note #4:** Appropriate reference/description/specifications (e.g., LOA) of certain specific components has been given.

**Note #5:** This DMF involves three different colorants that are considered adequate.

**Note #6:** Physician samples

**STATUS OF CONSULTS AND OTHER RELATED REVIEWS:**

ITEM	RECOMMENDATION	DATE	REVIEWER'S NAME
Microbiology	NA for oral tablet	NA	N/A
Inspection	Acceptable	5/30/01	Pat Alcock (HFD-320)
Methods Validation	To be conducted	NA	
OPDRA (Trade Name container/ carton labels)	Suggestions made	5/1/01 3/29/01	David Diwa Samie Beam
HFD-357 (N. Sager)	Acceptable (Fonsi of 4-17-01)	4-17-01	M. Maust
Biopharmaceutics	Dissolution issues resolved	3/23/01	E.O. Fadiran

21. **COMMENTS:** This review deals with the various outstanding control issues involved that include the applicant's response to the FDA Information Request letter dated May 24, 2001 and the response to certain labeling issues that have been addressed in response to Ms. Nguyen's requests to Dr. Nancy Price. Two response letters having the same date (May 30, 2001) were evaluated – one for CMC issues and the other for labeling issues.

22. **CONCLUSIONS AND RECOMMENDATIONS:** This NDA may be approved from a CMC perspective. All issues identified in earlier reviews have been satisfactorily addressed. The action letter should state the approved specifications for both drug substance and drug product impurities and dissolution. The applicant should also be requested to submit revised documentation for their approved specifications including their in-process Loss on Drying (LOD) limits in a timely manner.

/S/ 6-1-01

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Stuart Zimmerman, Ph. D.  
File: NDA21-283-CR#3

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

**NDA #21-283** DATE REVIEWED: 5/22/01

**REVIEW #: 2** REVIEWER: Stuart Zimmerman

<u>SUBMISSION TYPE</u>	<u>DOCUMENT</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	5/3/01	5/4/01	5/5/01
"	4/3/01	4/6/01	4/8/01
"	5/23/01	5/24/01	5/25/01

**NAME & ADDRESS OF APPLICANT:**

**DRUG PRODUCT NAME**

Proprietary: Diovan Tablets  
Established: Valsartan  
Code Name/#: Valsartan, CGP 48933

**CHEM. TYPE/THER. CLASS:** 3S

**PHARMACOL. CATEGORY/INDICATION:** Orally active angiotensin II antagonist

**DOSAGE FORM:** Tablet

**STRENGTHS:** 80 mg, 160 mg and 320 mg

**ROUTE OF ADMINISTRATION:** Oral

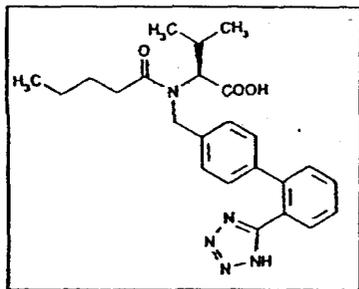
**Rx/OTC:** Rx Yes

**SPECIAL PRODUCTS:** No X

**CHEMICAL NAME, STRUCTURAL FORMULA:** (S)-N-Valeryl-N-{{2'-(1H-tetrazole-5yl)-biphenyl-4-yl}-methyl}-valine

Mol. Wt. = 435.5

Mol Formula : C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>



**SUPPORTING DOCUMENTS:**

- NDA 20-665 for Diovan Capsules
- NDA 20-818 for Diovan HCT Tablets

**DMFs (Type II):** The only Type II DMF involved is the one provided by the drug substance for which DMF is referenced in the NDA 20-665 for the Diovan Capsules. All the other synthetic operations are reported in the NDA 20-665 since ; facilities are involved.

**DMFs Involved:** This listing deals certain primary DMFs involved and cross reference to previously approved NDA 20-665 and 20-818 utilizations

DMF #	TYPE	HOLDER	ITEM REF.	STATUS CODE <sup>1</sup>	STATUS	DATE REVIEW	REVIEWER (NAME)
	III			1	OK	NA	NA
	III			1, 5	OK	NA	NA
	III			1	OK	NA	NA
	III			1	OK	NA	NA
	III			2	OK	NA	NA
	III			2, 3	OK	NA	NA
	III			1	OK	NA	NA
	III			3	OK	NA	NA
	III			6	OK	8/2/99	HFD-120 Christdoulous
	III			3	OK		N/A
	III			4	OK		NA
	III			4	OK		NA
	IV			5	OK	5/21/01	S Zimmerman

**Table Notes:** Extended evaluative comments are provided in the container-closure section of this review.

\*§ is the current name for this DMF  
 \*\* The firm was called. for NDA 20-818 – name change involved.

**Note #1:** Refer to Chemistry Review #1 for NDA 20-818 (p. 7) for reference to previously approved status.

**Note #2:** Refer to Chemistry Review #1 for NDA 20-665 for reference to previously approved status.

**Note #3:** Issue resolved concerning equivalency of. utilized

**Note #4:** Appropriate reference/description/specifications (e.g., LOA) of certain specific components has been given.

**Note #5:** This DMF involves three colorants that are considered adequate.

**Note #6:** Physician samples

**STATUS OF CONSULTS AND OTHER RELATED REVIEWS:**

ITEM	RECOMMENDATION	DATE	REVIEWER'S NAME
Microbiology	NA for oral tablet	NA	
Inspection	Acceptable	5/30/01	P. Alcock
Methods Validation	Awaiting potential specification changes	NA	
OPDRA (Trade Name container/ carton labels)	Suggestions given for container labels	5/1/01 3/29/01	David Diwa Samie Beam
HFD-357 (N. Sager)	Acceptable (Fonsi of 4-17-01)	4-17-01	M. Maust
Biopharmaceutics	Review completed with need to tighten dissolution limit.	3/23/01	E.O. Fadiran

21. **COMMENTS:** This review is a follow-up of some outstanding issues. The various facilities have been found to be acceptable by OC and FDA is awaiting a response to the information request letter that was sent on 5/25/01 as well as some labeling issues.
22. **CONCLUSIONS AND RECOMMENDATIONS:** This NDA is still not adequate from the standpoint of certain manufacturing controls and labeling issues. The issues involved need to be resolved in a timely manner.

S  
Stuart Zimmerman, Ph. D.  
File: NDA21-283-CR#2

5/31/01

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

**NDA #21-283** DATE REVIEWED: 5/22/01

**REVIEW #:** 1 **REVIEWER:** Stuart Zimmerman

<u>SUBMISSION TYPE</u>	<u>DOCUMENT</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	August 7, 2000	August 8, 2000	8/10/00

**NAME & ADDRESS OF APPLICANT:**

**DRUG PRODUCT NAME**

**Proprietary:** Diovan Tablets  
**Established:** Valsartan  
**Code Name/#:** Valsartan, CGP 48933

**CHEM. TYPE/THER. CLASS:** 3S

**PHARMACOL. CATEGORY/INDICATION:** Orally active angiotensin II antagonist

**DOSAGE FORM:** Tablet

**STRENGTHS:** 80 mg, 160 mg and 320 mg

**ROUTE OF ADMINISTRATION:** Oral

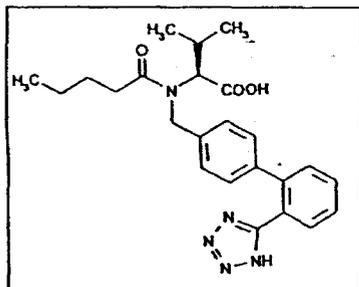
**Rx/OTC:** Rx Yes

**SPECIAL PRODUCTS:** No X

**CHEMICAL NAME, STRUCTURAL FORMULA :** (S)-N-Valeryl-N-{{2'-(1H-tetrazole-5yl)-biphenyl-4-yl}-methyl}-valine

Mol. Wt. = 435.5

Mol Formula : C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>



**SUPPORTING DOCUMENTS:**

- NDA 20-665 for Diovan Capsules
- NDA 20-818 for Diovan HCT Tablets

**DMFs (Type II):** The only Type II DMF involved is the one provided by the drug substance for which DMF is referenced in the NDA 20-665 for the Diovan Capsules. All the other synthetic operations are reported in the NDA 20-665 since Novartis facilities are involved.

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(pp. 4 - 55)

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# ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21283/000	Priority: 3S	Org Code: 110
Stamp: 08-AUG-2000 Regulatory Due: 08-JUN-2001	Action Goal:	District Goal: 09-APR-2001
Applicant: NOVARTIS PHARMS	Brand Name: DIOVAN (VALSARTAN) 80/160/320MG	
59 RT 10	TABLETS	
EAST HANOVER, NJ 079361080	Established Name:	
	Generic Name: VALSARTAN	
	Dosage Form: TAB (TABLET)	
	Strength: 80, 160, & 320 MG	
FDA Contacts: N. MORGENSTERN (HFD-110)	301-594-5300 , Project Manager	
S. ZIMMERMAN (HFD-110)	301-594-5300 , Review Chemist	
K. SRINIVASACHAR (HFD-110)	301-594-5376 , Team Leader	

## Overall Recommendation:

**ACCEPTABLE on 30-MAY-2001 by P. ALCOCK (HFD-324) 301-827-0062**

Establishment: 2416082  
NOVARTIS PHARMA INC (CIBA)  
OLD MILL RD  
SUFFERN, NY 10901

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 26-SEP-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE RELEASE  
TESTER

Establishment: 9692043  
NOVARTIS PHARMA INC (CIBA)  
SCHAFFHAUSERSTRASSE  
CH-4332 STEIN, , SZ

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-MAY-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MICRONIZER  
FINISHED DOSAGE  
MANUFACTURER

Establishment: 2210396  
NOVARTIS PHARMA INC (SANDOZ)  
59 RT 10  
EAST HANOVER, NJ 079361080

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 24-OCT-2000

Responsibilities: FINISHED DOSAGE RELEASE  
TESTER  
FINISHED DOSAGE STABILITY

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

## TESTER

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Establishment: **9611204** DMF No:  
**NOVARTIS PHARMA INC (SANDOZ)** AADA No:  
**LICHSTRASSE 35, ST. JOHANN SITE**  
**BASEL, , SZ 4002**

Profile: **CTL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE STABILITY**  
Last Milestone: **OC RECOMMENDATION** **TESTER**  
Milestone Date: **28-SEP-2000**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

---

Establishment: **9612715** DMF No:  
**NOVARTIS PHARMA INC (SANDOZ)** AADA No:  
**RINGASKIDDY/CORK, RINGASKIDDY**

Profile: **CTL** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE RELEASE**  
Last Milestone: **OC RECOMMENDATION** **TESTER**  
Milestone Date: **16-APR-2001**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

---

Establishment: DMF No:  
AADA No:

Profile: **TCM** OAI Status: **NONE** Responsibilities:  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **26-SEP-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

---

Establishment: DMF No:  
AADA No:

Profile: **TCM** OAI Status: **NONE** Responsibilities:

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Last Milestone: OC RECOMMENDATION  
Milestone Date: 26-SEP-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

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**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**ENVIRONMENTAL ASSESSMENT  
AND  
FINDING OF NO SIGNIFICANT IMPACT**

**FOR  
NDA 21-283**

**Diovan®**

**(Valsartan Tablets; 80, 160 and 320 mg)**

**Division of Cardio-Renal Drug Products (HFD-110)  
Center for Drug Evaluation and Research**

## **FINDING OF NO SIGNIFICANT IMPACT**

**NDA 21-283**

**Diovan®**

**(Valsartan Tablets; 80, 160 and 320 mg)**

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement is not required.

In support of their new drug application for Diovan® (Valsartan Tablets), 80, 160 and 320 mg, Novartis Pharmaceutical Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Valsartan is a chemically synthesized drug which is administered as a tablet in the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Investigation of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment. Based on these factors and the calculation of EIC, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

The results of toxicity studies indicate that the compound is not expected to affect organisms at the expected environmental concentrations. Therefore, no adverse environmental effects are expected to result from this action.

Diovan® (valsartan tablets), 80, 160 and 320 mg will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed drug product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages in accordance with their internal waste handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

April 14, 2001

DATE

ISI  
PREPARED BY

Melissa J. Maust

Chemist

Center for Drug Evaluation and Research

4/17/01

DATE

ISI  
CONCURRED BY

Nancy B. Sager

Environmental Officer

Center for Drug Evaluation and Research

4/17/01

DATE

ISI  
CONCURRED

Yuan-yuan Chiu, Ph.D.

Director, Office of New Drug Chemistry

Center for Drug Evaluation and Research

Attachment: Environmental Assessment

---

**DRA CMC Documentation****Diovan® Tablets  
(valsartan)****Environmental Assessment**

**Author(s):** Joyce Ann Sinno, Ph.D.  
**Document type:** Environmental Assessment  
**Document status:** Final  
**Release date:** 03-Aug-00  
**Number of pages:** 13

**Property of Novartis Pharmaceuticals Corporation**

## 1. Date

Original submission: document dated 03-Aug-00

Reference is also made to Environmental Assessments submitted to other Diovan NDAs:

**Diovan Capsules, Original NDA #20-665:** document dated 20-Nov-95  
Amendment, submitted 30-May-96  
Amendment, submitted 22-Oct-96.

**Diovan HCT Capsules, Original NDA #20-818:** document dated 18-Mar-97.

## 2. Name of Applicant/Petitioner

Novartis Pharmaceuticals Corporation

## 3. Address

59 Route 10  
East Hanover, NJ 07936-1080

## 4. Description of proposed action

### 4.1. Requested Approval

Novartis Pharmaceuticals Corporation has filed NDA 21-283 pursuant to section 505b of the FD&C Act for Diovan® (valsartan) Tablets, 80, 160 and 320 mg. All strengths are packaged in bottles of 30, 90 or 100 tablets, and in unit dose blister packages. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

### 4.2. Need for Action

Diovan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

### 4.3. Locations of Use

Patients with hypertension will use Diovan drug products in their homes, in clinics and in hospitals.

### 4.4. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

Rejected materials from the Novartis facility at Suffern, NY are incinerated at the American Ref-Fuel (Hempstead) Facility, 600 Avenue C, Westbury, NY 11590.

## 5. Identification of substances that are the subject of the proposed action

### 5.1. Nomenclature

#### 5.1.1. Established Name (U.S. Adopted Name – USAN)

Valsartan

#### 5.1.2. Brand/Proprietary Name/Tradename

Diovan®

#### 5.1.3. Chemical Names

##### Chemical Abstracts Index Name

L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

##### Systematic Chemical Name (IUPAC)

(*S*)-2-{*N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid

#### 5.1.4. Other names

CGP 48933 (research code)

### 5.2. Chemical Abstracts Service (CAS) Registration Number

137862-53-4

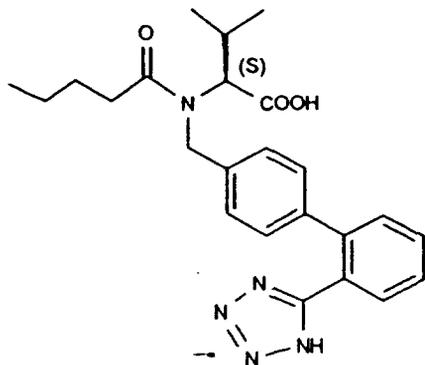
### 5.3. Molecular Formula

$C_{24}H_{29}N_5O_3$

### 5.4. Molecular Weight

435.5

## 5.5. Structural (graphic) Formula



## 6. Environmental issues

### 6.1. Physical and chemical characterization

Physical and chemical properties and constants were determined for Diovan drug substance, valsartan, and initially reported in Diovan 80 and 160 mg Capsules, Original NDA #20-665 (submitted 28-Dec-95; approved 23-Dec-96). For the convenience of the reviewer, this information is repeated in the present Environmental Assessment.

Studies to determine dissociation constant, water solubility, the octanol/water partition coefficient, vapor pressure, and ultraviolet-visible absorption were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*<sup>1</sup>.

The values obtained for each of these studies are presented in the Data Summary Table (Table 1) located at the end of this report. The full study reports were initially submitted in Diovan Capsules, Original NDA #20-665, and are again provided in the Confidential Appendices of this Assessment for the convenience of the reviewer.

#### 6.1.1. Dissociation constant (TAD Section 3.04)

The pK<sub>a</sub> value of valsartan was determined in CO<sub>2</sub>-free reagent water at 25°C. Under the conditions of this study, two pK<sub>a</sub>'s were determined: 3.76 (carboxylic group) and 5.60 (tetrazole group). Since valsartan has been shown to dissociate, water solubility and octanol/water partition coefficient were determined at pH 5, 7 and 9.

The mean pK<sub>a</sub>'s are reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.1. for the complete study report.

#### 6.1.2. Water solubility (TAD Section 3.01)

The mean solubility of valsartan was determined at 25°C in aqueous buffers at pH 5, 7 and 9. Valsartan was determined to have a pH-dependent solubility in water. Due to the solubility

and strong acidity of valsartan, the pH 7 and 9 buffer capacities were exceeded and the final values for pH were between 5.2 and 5.6. The mean solubility (N = 6) at each pH is reported as follows:

	pH 5	pH 7	pH 9
Mean solubility (mg/L)	2990	8210	1470
Standard deviation	196	430	186
Final pH range	5.2 - 5.6	5.2 - 5.6	5.2 - 5.6

The mean solubility of valsartan (mg/L) at each pH level is reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.2. for the complete study report.

### 6.1.3. n-Octanol/water partition coefficient (TAD Section 3.02)

The n-octanol/water partition coefficient ( $K_{ow}$ ) for valsartan was determined by the shake flask method using  $^{14}C$ -labeled material. Partitioning testing was conducted in triplicate at pH 5, 7 and 9 aqueous buffers at  $25 \pm 2$  °C using nominal concentrations of 0.001 and 0.0001 M in n-octanol-saturated buffer at each pH. The following mean values were observed:

pH	Initial Buffer Concentration moles/L	mean $K_{ow}$	Log P
5	$9.85 \times 10^{-4}$	32.2	1.51
	$1.07 \times 10^{-4}$	31.8	1.50
7	$1.04 \times 10^{-3}$	$6.78 \times 10^{-2}$	-1.17
	$1.09 \times 10^{-4}$	$9.83 \times 10^{-2}$	-1.01
9	$1.04 \times 10^{-3}$	$1.43 \times 10^{-2}$	-1.84
	$1.10 \times 10^{-4}$	$1.82 \times 10^{-2}$	-1.74

Based upon the mean  $K_{ow}$  and the log P [ $\log K_{ow}$ ] values obtained in this study, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb onto organic particles. Further, since the log  $K_{ow}$  was less than 3 at all pH levels tested, no further sorption/desorption properties ( $\log K_{ow}$ ) were considered.

The mean log n-octanol/water partition coefficient (log P) of valsartan at each pH level is reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.3. for the complete study report.

### 6.1.4. Vapor pressure (TAD 3.03)

The vapor pressure of valsartan was determined in triplicate by the gas saturation method at 25°C using nitrogen flow rates of 5, 10 and 20 ml/min over a period of 16 days. No valsartan was detected in the sorbent material at any of the flow rates. The detection limit of the instrumentation was therefore used to determine the vapor pressure of valsartan. The equilibrium vapor pressure of valsartan at 25°C was determined to be less than  $1.33 \times 10^{-5}$  Pa

at the nitrogen flow rate of 20 ml/min, or less than  $1.0 \times 10^{-5}$  torr. This corresponds to a Henry's Law Constant (H) less than  $1.30 \times 10^{-8}$ .

Based upon the Henry's Law Constant, valsartan would not be expected to be released into the air or have a significant vapor pressure.

The Henry's Law Constant for valsartan is reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.4. for the complete study report.

#### **6.1.5. Ultraviolet-visible absorption spectrum (TAD 3.05)**

Ultraviolet/visible spectra were obtained for valsartan at pH 5, 7 and 9. Valsartan in pH 5.00 buffer exhibited no absorption peaks. Absorption spectra in pH 7.01 buffer consisted of one major peak at 209 nm and two shoulders at 250 nm and 229 nm. Absorption spectra of valsartan in buffer at pH 8.96 consisted of one major peak at 207 nm and two shoulders at 229 nm and 251 nm.

The absorption spectra for valsartan are reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.5. for the complete study report.

### **6.2. Environmental depletion mechanisms**

Environmental depletion mechanisms were investigated for valsartan. Studies to determine hydrolysis and aerobic biodegradation were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*<sup>2</sup> as a guide.

#### **6.2.1. Aqueous hydrolysis rate constant and half-life (TAD Section 3.09)**

The first environmental depletion mechanism investigated was hydrolysis. Preliminary testing of <sup>14</sup>C-labeled valsartan was conducted over a 5-day period as per TAD, Section 3.09. Under the test conditions employed (50°C and all solutions removed from light), valsartan was determined to be hydrolytically stable at pH 5, 7 and 9 at 50°C. Based on these results, a half-life equal to or greater than one year at 25 °C was estimated using the criteria established in TAD, Section 3.09.

The hydrolysis half-life is reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.6. for the complete study report.

#### **6.2.2. Aerobic biodegradation (modified TAD Section 3.11)**

Since valsartan was considered to be hydrolytically stable, aerobic biodegradation was investigated as a potential depletion mechanism. The aerobic biodegradation of valsartan was determined in a batch-activated sludge (BAS) system. The method followed FDA TAD 3.11, with some modifications. Labeled test article was added to sludge obtained from a municipal wastewater treatment plant and aerobically incubated in the dark for 28 days at  $22 \pm 2$  °C. Since only slight transformation of the test article occurred with essentially no mineralization, the test was continued for another 10 days under these conditions. After 38 days, aeration to the system was discontinued, and the test system was incubated anaerobically for one month.

At the end of one month, the systems were again sampled and assayed. Again, no significant degradation of the test article or mineralization occurred during the anaerobic portion of the study. The BAS test system was validated by the reference test article, [<sup>14</sup>C]sodium benzoate, which resulted in approximately 80% evolved <sup>14</sup>CO<sub>2</sub> over the 28-day study.

Aerobic biodegradation in the wastewater treatment process may not be considered an important environmental depletion mechanism for valsartan.

The results of the biodegradation study are reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.7. for the complete study report.

### 6.3. Environmental concentration

#### 6.3.1. Expected Introduction Concentration (EIC)

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*<sup>3</sup>, the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

$EIC\text{-Aquatic (ppb)} = A \times B \times C \times D$ , where:

A = kg / yr produced for direct use (as active moiety)

B =  $1 / 1.214 \times 10^{11}$  liters per day entering POTWs [1996 Needs Survey, Report to Congress]

C = 1 year / 365 days per year

D =  $10^9$  µg/kg (conversion factor)

The EIC of valsartan has been calculated for the peak production year using estimates of Diovan drug substance requirements (Confidential Appendix 11.2.8.). The calculated EIC is provided in Confidential Appendix 11.2.9.

Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

### 6.4. Summary

#### 6.4.1. Aquatic environment

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Since valsartan exists as a di-anion with a double negative charge at physiological pH, the compound is very hydrophilic, and may therefore be a poor substrate for metabolizing enzymes.

A study using radiolabeled valsartan solution showed that valsartan is metabolized to a small extent only. The only notable metabolite detectable in the plasma is the valeryl-4-hydroxy valsartan (M1), an oxidized form of valsartan. Since this metabolite has not demonstrated any pharmacological activity *in vitro*, the biotransformation of valsartan to M1 can be described as an additional minor elimination process.

Valsartan is predominantly excreted as unchanged drug through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.

Studies were conducted to accurately determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at  $25 \pm 2$  °C. The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Tables 2 and 3 for the bioconcentration factor (BCF) and the soil adsorption coefficient ( $K_{oc}$ ) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in aqueous buffer solutions over the environmental pH range. Direct photodegradation would not be considered a potential mechanism of depletion.

Investigations of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment.

Five-year production estimates for Diovan drug products indicate that during the peak year, the EIC of valsartan at the point of entry into the aquatic environment will be greater than 1 ppb. Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

Based upon these factors, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

## 6.5. Environmental effects of released substances

The environmental effects of valsartan was evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA *Guidance for Industry*<sup>3</sup>). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02<sup>4</sup>. Additionally, since the Log  $K_{ow}$  was less than 3.5, acute toxicity testing was conducted in *Daphnia magna* utilizing TAD 4.08 from the US FDA *Environmental Assessment Technical Assistance Handbook*<sup>4</sup>. Both studies were conducted under FDA Good Laboratory Practices (GLPs).

### 6.5.1. Microbial inhibition test

The agar plate dilution method was used to evaluate the toxicity of valsartan to pure cultures of molds, ascomycetes, free-living nitrogen-fixing and soil bacteria, and blue-green algae. The minimum inhibitory concentrations (MIC) established for valsartan for these five representative cultures are:

Species	MIC (mg/L)
<i>Aspergillus niger</i>	> 1000
<i>Trichoderma viride</i>	> 1000
<i>Clostridium perfringens</i>	> 1000
<i>Bacillus subtilis</i>	1000
<i>Nostoc</i> sp.	200

Results indicate valsartan is non-inhibitory to microorganisms which may be found in activated sludge.

Results are reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.10. for the complete study report.

### 6.5.2. Acute toxicity in *Daphnia magna* (TAD 4.08)

With no depletion mechanism identified and with a  $\text{Log } K_{ow} < 3.5$ , a forty-eight hour acute toxicity study was conducted on one suitable test organism (an aquatic invertebrate) to further evaluate the ecotoxicity of valsartan, as described in the "Tiered Approach to Fate and Effects Testing".

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following the protocol described in *FDA Environmental Assessment Technical Assistance Handbook*, Document 4.08. Based on the results of this study, the 48-hour median effect concentration ( $\text{EC}_{50}$ ) for valsartan was estimated to be 580 mg/L, and the No-Observed-Effect-Concentration (NOEC) was determined to be 280 mg/L.

Results are reported in the Data Summary Table (Table 1). Please refer to Confidential Appendix 11.2.11. for the complete study report.

### 6.5.3. Assessment factor

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*<sup>3</sup>, an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (Maximum Expected Environmental Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 48-hour  $\text{EC}_{50}$  from the *Daphnia magna* study (Confidential Appendix 11.2.11.) and the calculation of the EIC (Confidential Appendix

11.2.9.), an Assessment Factor of [ $\ggg 10,000$ ] is obtained. (Calculation of the Assessment Factor is provided in Confidential Appendix 11.2.12.) Thus, no additional ecotoxicity testing is required for valsartan. Since the Assessment Factor calculated for valsartan is significantly more than one order of magnitude greater than that reported in the Guidance Document, the results suggest valsartan would be nontoxic in the aquatic environment.

## 7. Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis Pharmaceuticals has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Diovan drug products within the United States. No mitigation measures are considered necessary.

## 8. Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of Diovan drug products. The use of Diovan drug products will directly benefit patients suffering from hypertension.

It is our conclusion that approval of this Application is therefore preferable to non-approval.

## 9. List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in Non-confidential Appendix 11.1.1.

## 10. References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.
2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).
3. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), July 1998. Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1.
4. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.

## 11. Appendices

### 11.1. Non-confidential appendices

11.1.1. Curriculum vitae of contributors

### 11.2. Confidential appendices

11.2.1. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of dissociation constant. Technical Assistance Document, Section 3.04, Study 1781.1294.6476.855, dated 05-Sep-95.

11.2.2. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of water solubility. Technical Assistance Document, Section 3.01, Study 1781-1294-6472-700, dated 08-Aug-95.

11.2.3. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of n-octanol/water partition coefficient. Technical Assistance Document, Section 3.02, Study 1781.1294.6474.705, dated 09-Aug-95.

11.2.4. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of vapor pressure. Technical Assistance Document, Section 3.03, Study 1781.1294.6475.740, dated 05-Sep-95.

11.2.5. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of the ultraviolet-visible absorption spectrum in aqueous solution. Technical Assistance Document, Section 3.05, Study 1781.1294.6477.850, dated 09-Aug-95.

11.2.6. Springborn Laboratories, Inc., Valsartan (<sup>14</sup>C-CGP 48933) – Determination of hydrolysis in water. Technical Assistance Document, Section 3.09, Study 1781.1294.6480.715, dated 05-Sep-95.

11.2.7. Springborn Laboratories, Inc., Valsartan ([<sup>14</sup>C]CGP 48933) – Aerobic biodegradation in activated sludge. Technical Assistance Document, Section 3.11, Study 1781.1294.6481.799, dated 05-Sept-95.

11.2.8. Production estimates of Diovan drug substance requirements.

11.2.9. Expected Introduction Concentration (EIC) of valsartan based upon production estimates.

11.2.10. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Determination of microbial growth inhibition. Technical Assistance Document, Section 4.02, Study 1781.1294.6473.770, dated 08-Aug-95.

11.2.11. Springborn Laboratories, Inc., Valsartan (CGP 48933) – Acute toxicity to daphnids (*Daphnia magna*) under static conditions. Technical Assistance Document, Section 4.08, Study 1781.1294.6482.110, dated 08-Aug-95.

11.2.12. Calculation of Assessment Factor

Table 1. Data Summary Table

DATA SUMMARY TABLE		
<b>PHYSICAL / CHEMICAL CHARACTERIZATION</b>		
Water Solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9	
Dissociation Constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)	
Log n-Octanol/Water Partition Coefficient (Log K <sub>ow</sub> )	1.51 @ pH 5 in 9.85 x 10 <sup>-4</sup> moles/L buffer 1.50 @ pH 5 in 1.07 x 10 <sup>-4</sup> moles/L buffer -1.17 @ pH 7 in 1.04 x 10 <sup>-3</sup> moles/L buffer -1.01 @ pH 7 in 1.09 x 10 <sup>-4</sup> moles/L buffer -1.84 @ pH 9 in 1.04 x 10 <sup>-3</sup> moles/L buffer -1.74 @ pH 9 in 1.10 x 10 <sup>-4</sup> moles/L buffer	
Henry's Law Constant (H)	< 1.30 x 10 <sup>-8</sup>	
Ultraviolet-visible absorption spectrum	No absorption peaks @ pH 5. One main peak at 209 nm @ pH 7. One main peak at 207 nm @ pH 9.	
<b>DEPLETION MECHANISMS</b>		
Hydrolysis	t <sub>1/2</sub> ≥ 1 year at 25 °C	
Aerobic Biodegradation	0.02 % <sup>14</sup> C evolved over 28-day aerobic study	
Metabolism	Valsartan is predominantly excreted unchanged through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.	
<b>ENVIRONMENTAL EFFECTS</b>		
Microbial Inhibition	<b>Species</b>	<b>MIC (mg/L)</b>
	<i>Aspergillus niger</i>	> 1000
	<i>Trichoderma viride</i>	> 1000
	<i>Clostridium perfringens</i>	> 1000
	<i>Bacillus subtilis</i>	1000
	<i>Nostoc</i> sp.	200
Acute Toxicity in <i>Daphnia magna</i>	EC <sub>50</sub> = 580 mg/L.	
	NOEC = 280 mg/L	

### Calculated environmental fate results

**Table 2. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient ( $K_{oc}$ ) for valsartan based upon experimentally determined mean water solubility (Confidential Appendix 11.2.2.)**

	pH 5	pH 7	pH 9
Water solubility (mg/L)	2990	8210	1470
BCF <sup>a</sup>	6.77	3.83	2.76
$K_{oc}$ <sup>b</sup>	53.5	30.7	22.3

<sup>a</sup>  $\text{Log (BCF)} = 2.791 - 0.564 \text{ Log (S)}$ , where S = water solubility in mg/L.

<sup>b</sup>  $\text{Log (}K_{oc}\text{)} = 3.64 - 0.55 \text{ Log (S)}$ , where S = water solubility in mg/L.

**Table 3. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient ( $K_{oc}$ ) for valsartan based upon experimentally determined partition coefficient (log  $K_{ow}$ ) (Confidential Appendix 11.2.3.)**

	Range	
	Low	High
BCF <sup>a</sup>	0.0135X	6.32X
$K_{oc}$ <sup>b</sup>	2.32	160

The highest (-1.86) and lowest (1.52) log  $K_{ow}$  values were used to calculate the BCF and  $K_{oc}$ .

<sup>a</sup>  $\text{Log (BCF)} = (0.79 \times \text{log } K_{ow}) - 0.40$  (Kenaga and Goring, 1980)

<sup>b</sup>  $\text{Log (}K_{oc}\text{)} = (0.544 \times \text{log } K_{ow}) + 1.377$  (Kenaga and Goring, 1980)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-283**

**Clinical Pharmacology and Biopharmaceutics  
Review**

# CLINICAL PHARMACOLOGY/BIOPHARMACEUTIC REVIEW

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NDA: 21-283  
Diovan<sup>®</sup> (Valsartan) Tablets  
(80, 160 & 320 MG )

SUBMISSION DATE: AUGUST 7, 2000  
OCTOBER 10, 2000

NOVARTIS PHARMACEUTICALS

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NDA (NEW DOSAGE FORM)

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## EXECUTIVE SUMMARY

Valsartan is a synthetic angiotensin II receptor antagonist approved for the treatment of hypertension and is currently available as 80 and 160 mg capsules (Diovan™ Capsules, NDA 20-665 approved December 23, 1996). It is also available as combination film-coated tablets consisting of valsartan/Hydrochlorothiazide 80/12.5 and 160/12.5 mg (Diovan HCT, NDA 20-818).

The sponsor has submitted an original NDA to provide for a new formulation of Diovan® (valsartan) which is intended to replace the current capsule formulation. This switch from the presently marketed capsule to a tablet formulation is intended to enhance both patient acceptance and the production process. This submission includes an individual dosage form for the 320 mg strength. While Diovan 320 mg was not available as a single capsule the current labeling states that "Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day." Accordingly, reference is made to NDA 20-665 for clinical data supporting use of valsartan 320 mg.

The sponsor has submitted two bioavailability/bioequivalence studies. The relative bioavailability of two revised valsartan tablet formulations was tested in a pilot bioavailability study at a dose of 160 mg, using the 160 mg capsule as a reference (Study CVAL489 0603). On the basis of the results of this pilot study, the variant with reduced crospovidone content was chosen for further development. Four tablet strengths (40 mg, 80 mg, 160 mg, and 320 mg) with a proportionally identical composition were produced at the same manufacturing site. A definitive trial was carried out to demonstrate bioequivalence at the highest dose strength of 320 mg between the tablet formulation variant with reduced crospovidone content selected in the pilot BA study, and the marketed capsules (Study CVAL489 0604). The data obtained from this study confirm the bioequivalence of the 320 mg valsartan tablet and 2 x 160 mg marketed valsartan capsules.

The sponsor has requested for a waiver of bioequivalence study for the lower strengths of 80 and 160 mg based on similar *in vitro* dissolution profiles for all dose strengths in three different dissolution media (pH 1.0, pH 4.5, pH 6.8). A waiver of the bioequivalence study requirement for the 80 and 160 mg tablet strengths of Diovan® tablets is granted.

Measurement of valsartan in human plasma was accomplished using a validated

An acceptable *in vitro* dissolution method has been provided but the dissolution specification should be changed from not less than % at (Q= ) minutes to not less than % at minutes (Q= ) for valsartan.

### COMMENT TO BE SENT TO THE SPONSOR:

DISSOLUTION: The proposed dissolution specification of at least % in min is not

acceptable. Based on the dissolution data submitted to the NDA it is recommended that the dissolution specification should be changed to *not less than* % at min (i.e. Q= % in min) for valsartan.

**RECOMMENDATIONS:**

The Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology & Biopharmaceutics (OCPB) has completed the review of the sponsor's NDA 21-283 and recommends that:

- The dissolution method developed by the sponsor is acceptable but the dissolution specification should be changed as mentioned above.
- The sponsor's request for a waiver of bioequivalence study for the lower strengths of 80 and 160 is granted.
- The draft labeling is acceptable to OCPB
- Please forward the above comment to the sponsor.

/s/

Emmanuel O. Fadiran, Ph.D.  
Division of Pharmaceutical Evaluation I

FT Initialed by A. Dorantes, Ph.D. -----

CPB Briefing Day 03/23/2001 (Mehta, Sahajwalla, Dorantes, Fadiran, Nguyen, Chou)

cc: NDA 21-283, HFD-110, HFD-860 (Fadiran, Dorantes, Mehta), BIOPHARM – CDR.

**QUESTION BASED REVIEW**

**1. How were the new tablet formulations developed?**

The relative bioavailability of two revised valsartan tablet formulations was tested in a pilot bioavailability study at a dose of 160 mg, using the 160 mg capsule as a reference (Study CVAL489 0603). The ratios of the least square means for  $AUC_{0-t}$ ,  $AUC_{all}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  indicate that absorption from the 160 mg tablet with reduced avicel content was on average 12 to 13 % higher, and from the 160 mg tablet with reduced crospovidone content 8 to 9 % higher compared with the 160 mg capsule. For both test treatments the estimated difference in bioavailability compared with the reference treatment was not statistically significant. On the basis of the results of this pilot study, the variant with reduced crospovidone content was chosen for further development. Four tablet strengths (40 mg, 80 mg, 160 mg, and 320 mg) with a proportionally identical composition were produced at the same manufacturing site (see Composition of the Formulations below).

**2. Is the highest dose strength of the new tablet formulation bioequivalent to the approved 2x160 mg marketed capsule formulation?**

A definitive trial was carried out to demonstrate bioequivalence at the highest dose strength of 320 mg between the tablet formulation variant with reduced crospovidone content selected in the pilot BA study, and 2x160 mg of the approved Diovan capsules (Study CVAL489 0604). The 90% confidence intervals of the  $AUC_{0-\infty}$  and  $C_{max}$  parameters were within the range of \_\_\_\_\_ and confirm the bioequivalence of the 320 mg valsartan tablet and 2 x 160 mg marketed valsartan capsules.

**3. Should the sponsor's request for waiver of bioequivalence study for the 80 and 160 mg tablet formulations be granted?**

The sponsor has requested for a waiver of bioequivalence study for the lower strengths of 80 and 160 in accordance with 21 CFR 320.22(d)(2) for drug products that are in the same dosage form and are proportionally similar in their active and inactive ingredients. This waiver request is supported by:

- The proportional composition of all tablet strengths
- Evidence of linear pharmacokinetics for valsartan demonstrated in the original application for Diovan™ Capsules (NDA 20-665)
- Similar *in vitro* dissolution profiles (see Drug Product Dissolution Testing below) for all dose strengths in three different dissolution media (pH 1.0, pH 4.5, pH 6.8).

A waiver of the bioequivalence study requirement for the 80 and 160 mg tablet strengths of Diovan® tablets is therefore granted.

**4. What assay method was used to determine valsartan plasma concentrations?**

Measurement of valsartan in human plasma was accomplished using a \_\_\_\_\_  
The limit of quantitation (LOQ)  
was generally set to \_\_\_\_\_ mg/L. Assay was fully validated, and study validation data are provided in each study report.

**5. Has the sponsor developed a satisfactory dissolution method and proposed a satisfactory dissolution specification for the new valsartan tablet formulations?**

An acceptable in vitro dissolution method has been provided but the proposed dissolution specification of at least 75% in 15 min is not acceptable. It is recommended that the dissolution specification should be changed to *not less than 75% at 15 min (i.e. Q= 75% in 15 min)* for valsartan (see Drug Product Dissolution Testing below).

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**COMPOSITION OF THE FORMULATIONS**

The nominal composition of each dosage form and the function of each excipients in the formulation is shown in the following table.

**Composition of Diovan 80, 160 and 320 mg film-coated tablets**

Ingredient	Amount per tablet (mg)			Function	Reference to standard
	80mg	160mg	320mg		
<b>Core</b>					
Valsartan	80.0	160.0	320.0	Active ingredient	Novartis monograph
Microcrystalline Cellulose					NF
Crospovidone					NF
Colloidal Anhydrous Silica					NF
Colloidal silicon Dioxide					NF
Magnesium Stearate					NF
<b>Core weight</b>					
<b>Coating</b>					
					Novartis monograph
Purified Water <sup>2</sup>	-	-	-		USP
<b>Total Tablet Weight</b>	<b>161.0</b>	<b>319.0</b>	<b>636.0</b>		

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the approval package consisted of draft labeling

pp. 9-18

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**INDIVIDUAL STUDY REVIEW**

**BIOAVAILABILITY/BIOEQUIVALENCE STUDY**

**STUDY NUMBER:** CVAL489 0603

**VOLUME:** 1.9

**PAGES:** 6-1 – 6-294

**STUDY TITLE:** A single center, open-label, three-period, randomized crossover pilot study to investigate relative bioavailability of 2 different tablet formulations of valsartan compared to the marketed valsartan 160 mg capsule

**INVESTIGATOR AND LOCATION:** Michael Seiberling, M.D.  
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Switzerland

**STUDY PERIOD:** AUGUST 10-30, 1999

**OBJECTIVE:** To investigate relative bioavailability of 2 different tablet formulations of valsartan (modified 160 mg tablet formulation with reduced avicel content = Treatment A; modified 160 mg tablet formulation with reduced crospovidone content = Treatment B) compared to the 160 mg marketed valsartan capsule (Treatment C) in healthy subjects.

**FORMULATIONS:**

Modified valsartan tablet 160 mg, reduced avicel content (Batch No CH. B 990031); modified valsartan tablet 160 mg, reduced crospovidone content (Batch No CH. B 990032).  
Diovan® capsule 160 mg (marketed; Batch No CH. 023800)

**STUDY DESIGN:** This pilot study employed a single center, open-label, three-treatment, three-period, randomized crossover design. Initially 12 healthy male and female subjects were enrolled in this study. After an overnight fast, each subject received 160 mg of valsartan either as a tablet (Treatments A, B) or as a capsule (Treatment C). Blood samples were collected according to the following schedule: predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose.

**ASSAYS:**

**VALSARTAN -**

Linearity: Satisfactory. Standard curves from to mg/ml.

Accuracy: Satisfactory. % at mg/ml, % at mg/ml and % at mg/ml.

Precision: Satisfactory. % at mg/ml, % at mg/ml and % at mg/ml.

Sensitivity: LOQ - mg/L.

The assay has been validated over the range of valsartan plasma concentrations observed in the study.

**DATA ANALYSIS:** Assessment and comparison between the 3 treatments of the respective values of AUC<sub>all</sub>, AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, t<sub>max</sub>, and t<sub>1/2</sub>.

**RESULTS:** Tables 1 and 2 summarize the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the three treatments.

**Table 1. Summary of the main pharmacokinetic parameters after a single dose administration of the three 160 mg valsartan formulations**

Treatment	$t_{max}$	$C_{max}$	*AUC <sub>all</sub>	AUC <sub>0-∞</sub>	$t_{1/2}$
	(h)	(mg/L)	(h•mg/L)	(h•mg/L)	(h)
	median (min; max) ± SD (CV%)	mean ± SD (CV%)	mean ± SD (CV%)	mean ± SD (CV%)	mean ± SD (CV%)
A (tablet with reduced avicel content)	2.00 (1.00, 3.00)	6.001 ± 1.806 (30.1)	32.037 ± 11.627 (36.3)	32.684 ± 11.593 (35.5)	12.68 ± 6.84 (53.9)
B (tablet with reduced crosopovidone content)	2.50 (1.50, 3.00)	5.642 ± 1.876 (33.2)	30.973 ± 10.553 (34.1)	31.576 ± 10.541 (33.4)	11.78 ± 5.96 (50.6)
C (marketed valsartan capsule)	2.50 (1.50, 3.00)	5.672 ± 2.472 (43.6)	29.273 ± 11.516 (39.3)	29.723 ± 11.543 (38.8)	10.22 ± 3.93 (38.4)

\*AUC<sub>all</sub>: Area under the concentration-time curve (AUC) from time zero to the time of the last observation calculated by the linear/log trapezoidal method. If the last concentration is non-zero AUC<sub>0-t</sub> = AUC<sub>all</sub>. Otherwise AUC<sub>all</sub> will be greater than AUC<sub>(0-t)</sub> as it includes the additional area from the last measurable concentration down to zero

**Table 2. Summary analysis of least squares means for valsartan pharmacokinetic parameters (all completed subjects with evaluable parameters on both treatments)**

Treatment	Parameter	Least squares mean (N)	Ratio of least square means (test / reference)**	90% confidence interval for ratio of least squares means***
Treatment A 160 mg tablet reduced avicel	AUC <sub>0-t</sub>	29.78 (12)	1.12	(0.96, 1.31)
	AUC <sub>all</sub>	30.09 (12)	1.12	(0.96, 1.31)
	AUC <sub>0-∞</sub>	30.80 (12)	1.13	(0.97, 1.32)
	$C_{max}$	5.72 (12)	1.12	(0.93, 1.34)
Treatment B 160 mg tablet reduced crosopovidone	AUC <sub>0-t</sub>	28.77 (12)	1.09	(0.93, 1.27)
	AUC <sub>all</sub>	29.03 (12)	1.08	(0.93, 1.26)
	AUC <sub>0-∞</sub>	29.67 (12)	1.09	(0.93, 1.27)

Treatment	Parameter	Least squares mean* (N)	Ratio of least square means (test / reference)**	90% confidence interval for ratio of least squares means***
	$C_{max}$	5.34 (12)	1.04	(0.87, 1.25)
Treatment C 160 mg capsule marketed	$AUC_{0-t}$	26.49 (12)		
	$AUC_{all}$	26.78 (12)		
	$AUC_{0-\infty}$	27.25 (12)		
	$C_{max}$	5.13 (12)		

N represents the number of observations.

\* The least squares means are expressed on the original (anti-log) scale

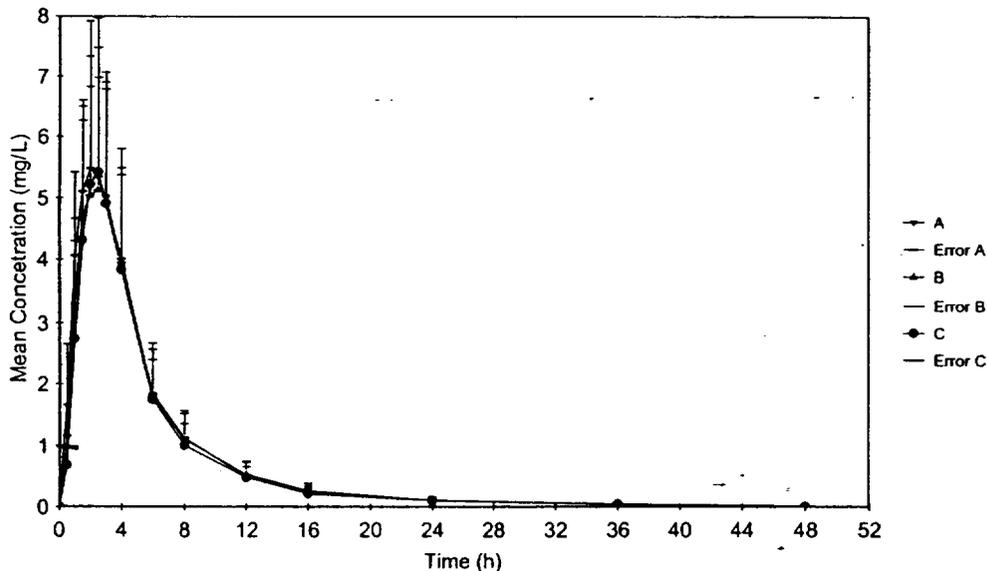
\*\* The ratio of means on the original scale is estimated by the antilog of the difference in least squares means on the log scale; reference treatment = Treatment C:

\*\*\* The confidence interval for the ratio of the tablet to capsule on the original scale is obtained by taking the anti-logs of the confidence limits for the difference of the treatment least squares means on the log scale.

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**Figure 1. Mean concentration-time profiles of valsartan with 3 different 160 mg formulations**

The upper error bars (SD) are shown and the protocol time is used for clarity. Treatment A = 160 mg tablet with reduced avicel content; Treatment B = 160 mg tablet with reduced crospovidone content; Treatment C = 160 mg marketed valsartan capsule.



**CONCLUSIONS:**

- The results of this pilot study with two new variants of a valsartan tablet formulation, one with reduced relative content of avicel and the other one with reduced content of crospovidone, suggest that for both test formulations there is a reasonable chance to claim bioequivalence with respect to the marketed capsule in a further well-powered confirmatory trial.
- The tablet variant with reduced content of crospovidone was proposed for further development because of slightly more favorable pharmacokinetic characteristics compared to the variant with reduced avicel content: same  $t_{max}$  as the Diovan capsule, AUC and  $C_{max}$  ratios closer to one, smaller variability of PK parameters.

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**BIOEQUIVALENCE STUDY**

**STUDY NUMBER:** CVAL489 0604      **VOLUMES:** 1.10-1.11

**STUDY TITLE:** A single center, open-label, two-treatment, three-period, repeated-measure, randomized crossover study to establish bioequivalence of a new valsartan 320 mg tablet and 160

mg marketed valsartan capsules

**INVESTIGATOR AND LOCATION:** Rainer Schulz, MD  
Quintiles GmbH, Freiburg, Germany

**STUDY PERIOD:** January 13 – February 20, 2000

**OBJECTIVE:** To establish bioequivalence of a new valsartan 320 mg tablet (Treatment A) and 2x160 mg marketed Diovan® capsules (Treatment B) in healthy subjects.

**FORMULATIONS:**

Valsartan tablet 320 mg (Batch No. X361 1199)  
Diovan® capsule 160 mg (marketed; Batch No. 023800)

**STUDY DESIGN:**

The study employed a single center, open-label, two-treatment, three-period, repeated-measure, randomized crossover design with 40 healthy (21 males / 19 females) subjects. In every treatment sequence, the treatment of the second period was repeated\* in the third period (i.e., ABB or BAA). Subjects were allocated at random to one of the two treatment sequences. There was a minimum 3-day washout phase between treatments. All treatments were administered after at least a 10-hour overnight fast. Fasting was continued for 4 hours after dosing.

Blood samples were collected according to the following schedule: predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose.

**ASSAYS:**

**VALSARTAN -**

Linearity: Satisfactory. Standard curves from to mg/ml.  
Accuracy: Satisfactory. % at mg/ml, % at mg/ml and % at mg/ml.  
Precision: Satisfactory. % at mg/ml, % at mg/ml and % at mg/ml.  
Specificity: Satisfactory. submitted.  
Sensitivity: LOQ - mg/L.

The assay has been validated over the range of valsartan plasma concentrations observed in the study.

**DATA ANALYSIS:** AUC<sub>0-48</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, t<sub>1/2</sub>, and T<sub>max</sub>, were calculated.

**Statistical methods:** For comparisons of means, parametric analyses were performed on AUC<sub>0-t</sub>, AUC<sub>all</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub>, using log-transformed values. For each of these parameters, an analysis of variance model was fit to data containing the factors sequence, subject within sequence, treatment and period using the Statistical Analysis System (SAS); procedure with subject being a random term in the model. The 90% confidence limits for the

difference between least squares means on the log-scale were anti-logged to provide 90% confidence limits for the ratio of the two least squares means on the original untransformed scale.

**RESULTS:** Tables 1 and 2 summarize the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments.

**Table 1: Summary of the main pharmacokinetic parameters of valsartan after a single dose administration of the new 320 mg tablet vs the 2x160 mg marketed capsules**

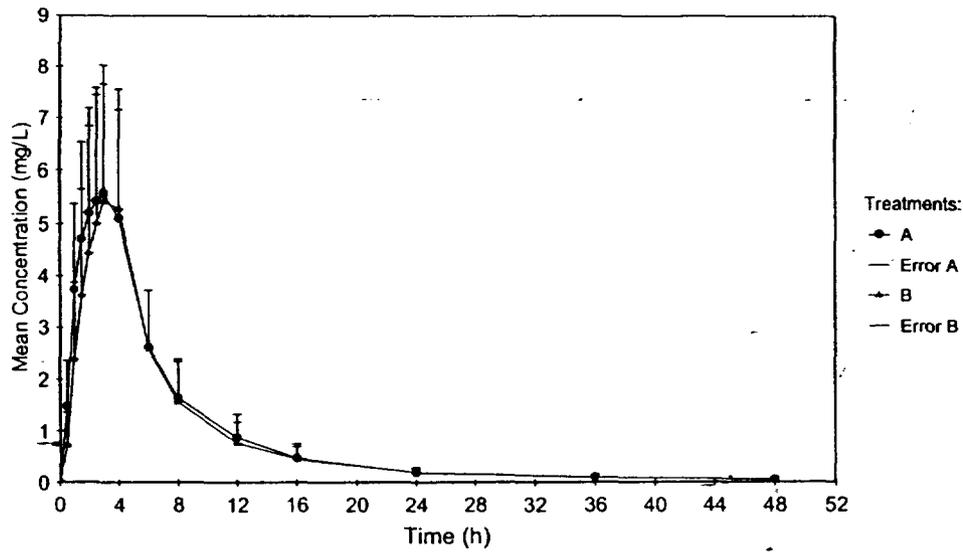
Treatment	$t_{max}$ (h) median (min; max)	$C_{max}$ (mg/L) mean ± SD (CV%)	$AUC_{0-t}$ (h•mg/L) mean ± SD (CV%)	* $AUC_{all}$ (h•mg/L) mean ± SD (CV%)	$AUC_{0-∞}$ (h•mg/L) mean ± SD (CV%)	$t_{1/2}$ (h) mean ± SD (CV%)
A (new valsartan 320 mg tablet)	2.75 (1.00, 4.37)	6.162 ± 2.098 (34.0)	41.050 ± 13.449 (32.8)	41.108 ± 13.441 (32.7)	42.683 ± 13.219 (31.0)	14.69 ± 9.62 (65.5)
B (2x160 mg marketed valsartan capsules)	3.00 (1.00, 6.00)	6.164 ± 2.508 (40.7)	38.110 ± 15.407 (40.4)	38.202 ± 15.376 (40.3)	39.829 ± 15.691 (39.4)	14.56 ± 9.51 (65.3)

\* $AUC_{all}$ : Area under the concentration-time curve (AUC) from time zero to the time of the last observation calculated by the linear/log trapezoidal method. If the last concentration is non-zero  $AUC_{0-t} = AUC_{all}$ . Otherwise  $AUC_{all}$  will be greater than  $AUC_{(0-t)}$  as it includes the additional area from the last measurable concentration down to zero

**Figure 1: Mean concentration-time profiles of valsartan after a single dose of the new 320 mg tablet vs the 2x160 mg marketed capsules**

The upper error bars (SD) are shown and the protocol time is used for clarity.  
Treatment A = 320 mg valsartan tablet; Treatment B = 2x160 mg marketed valsartan capsule

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**Statistical results:** Parameters are summarized in Table 2:

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Table 2: Summary analysis of least squares means for valsartan pharmacokinetic parameters

Parameter	320 mg tablet (Treatment A) Least squares mean* (N)	2*160 mg capsules (Treatment B) Least squares mean* (N)	Ratio of least square means** (N)	90% confidence interval for ratio of least squares means***
$C_{max}$	5.95 (60)	5.47 (60)	1.09 (60)	(0.98, 1.21)
$AUC_{0-t}$	38.84 (60)	35.14 (60)	1.11 (60)	(1.02, 1.20)
$AUC_{all}$	38.92 (60)	35.24 (60)	1.10 (60)	(1.02, 1.20)
$AUC_{0-\infty}$	40.53 (60)	36.93 (60)	1.10 (60)	(1.02, 1.19)

N represents the number of observations including repeated dosing.

\* The least squares means are expressed on the original (anti-log) scale

\*\* The ratio of means on the original scale is estimated by the antilog of the difference in least squares means on the log scale.

\*\*\* The confidence interval for the ratio of the tablet to capsule on the original scale is obtained by taking the anti-logs of the confidence limits for the difference of the treatment least squares means on the log scale.

**CONCLUSION:** The data obtained from the study showed that the new Diovan tablet formulation at a dose of 320 mg valsartan is bioequivalent to the marketed Diovan® capsule 2x160 mg.

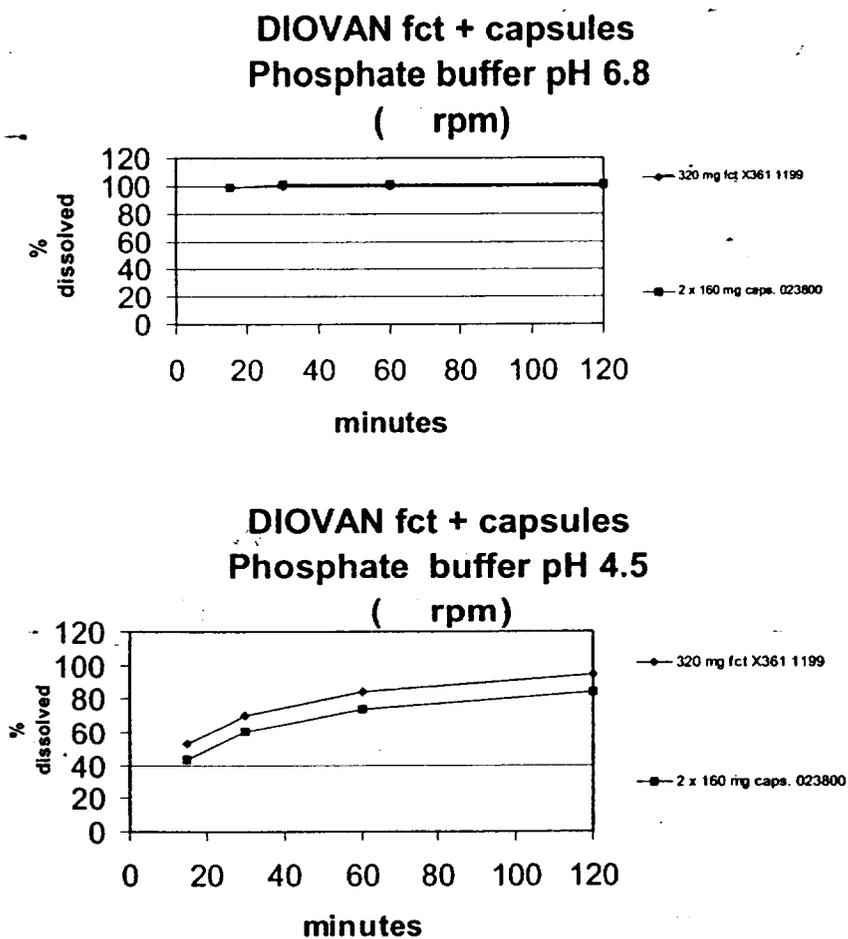
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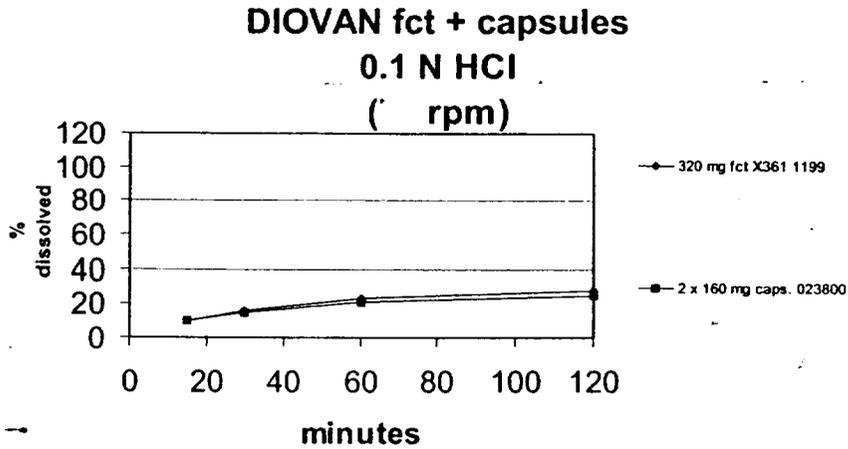
**DRUG PRODUCT DISSOLUTION TESTING**

### Dissolution profiles of the 320 mg tablet vs the 2 x 160 mg marketed capsules

In vitro dissolution tests were performed with the batches of the test and the reference products that were used in the pivotal BE trial (Study\_CVAL4890604). Mean dissolution profiles of Diovan 320 mg film-coated tablets (fct) vs the 2 x 160 mg capsules in three different media are depicted in Figure 1 and values of the  $f_2$  similarity factor are listed in Table 1.

Figure 1. Dissolution profiles of Diovan 320 mg film-coated tablets (fct) vs the 2 x 160 mg capsules in three different media (n = 12)





**Table 1.  $f_2$  similarity factors comparing dissolution profiles of the 320 mg tablets and the 2 x 160 mg marketed capsules**

	pH of medium		
	6.8	4.5	1.0
$f_2$ similarity factors	N/A *	51	86

\* No  $f_2$  values were calculated for the profile comparison at pH 6.8 as, for each dissolution profile determined, more than one value exceeds 10% of declared content.

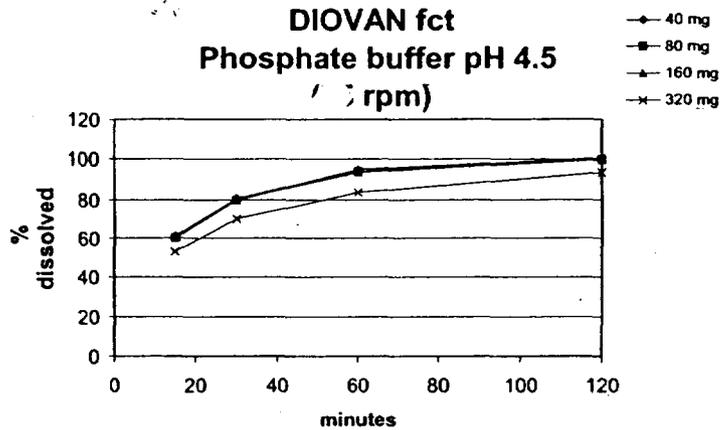
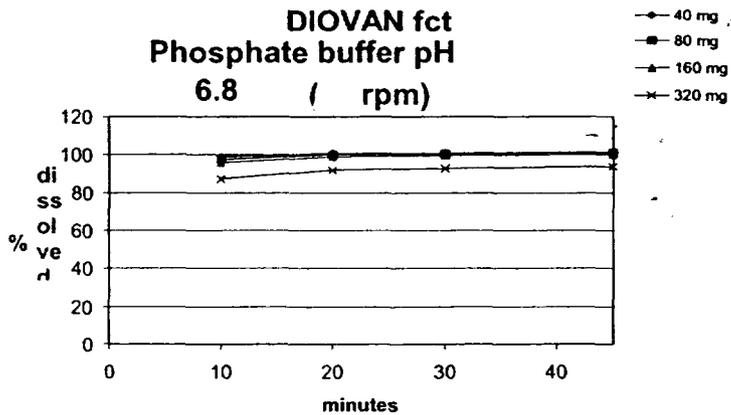
Mean dissolution profiles of the test and the reference product were overall similar and in 2 media (pH 6.8 and pH 1) the mean dissolution curves appeared closely matching.

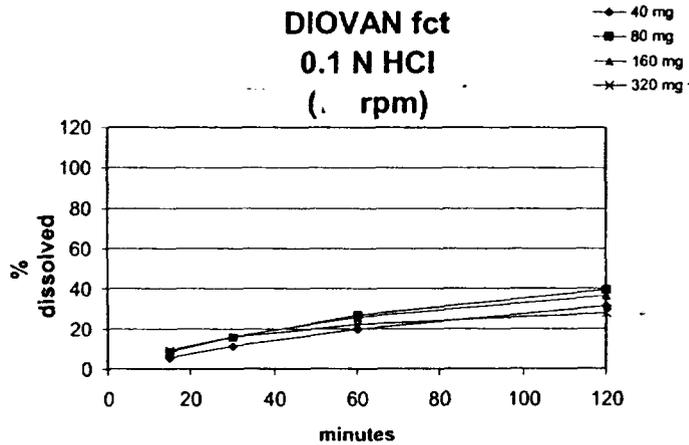
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### Dissolution profiles of the 40, 80, and 160 mg tablet vs the 320 mg tablet

Dissolution profiles of the lower dose strengths of 40, 80, and 160 mg of the tablet formulation vs the highest dose strength of 320 mg were performed to show similar performance in terms of in vitro dissolution across the entire dose range. The batch of the 320 mg tablet used for the dissolution profiles was the same as the batch used in BE study (Protocol 604).

Figure 1. Dissolution profiles of Diovan 40 mg, 80 mg, 160 mg and 320 mg film-coated tablets (fct) in three different media (n = 12)





**Table 2.  $f_2$  similarity factors comparing dissolution profiles of the 320 mg strength to the 40 mg, 80 mg, and 160 mg strengths**

$f_2$ similarity factors versus 320 mg profile	pH of medium		
	6.8	4.5	1.0
40 mg	N/A *	54	70
80 mg	N/A *	53	60
160 mg	N/A *	53	66

\* No  $f_2$  values were calculated for the profile comparisons at pH 6.8 as, for each dissolution profile determined, more than one value exceeds 10% of declared content.

Mean dissolution profiles of the test and the reference product were overall similar in all the three dissolution media tested. Rapid dissolution for all doses observed at pH 6.8 and  $f_2$  values confirm the similarity of the tablet formulation in terms of in vitro dissolution.

#### Dissolution in other media

The media of pH 4.5 and pH 1.0 were explored but were found to be of limited suitability for the

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valsartan drug substance because of the following observations:

- No sink conditions exist for any strength at pH 1.0, valsartan is poorly soluble at pH 1.0
- Around pH 4.5 the drug substance is very sensitive to small shifts in pH which affects the method ruggedness.
- The methods using pH 4.5 medium is overdiscriminative. For formulations for which bioequivalence has been demonstrated the dissolution curves at pH 4.5 may display significant differences and low  $f_2$  factor (Figure 1 and Table 1 above).

Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength: Film-coated tablets, 80, 160 and 320 mg Valsartan

Dissolution Apparatus: USP Dissolution Apparatus II (paddle)

Dissolution Medium: 0.067 M Phosphate Buffer, pH 6.8, degassed, at  $37 \pm 0.5^\circ\text{C}$

Volume 1000 ml

Speed of Rotation:

Sampling Time:

Procedure: Determine the amount of valsartan dissolved from UV absorbance at 250 nm.

Recommended Specification: At least % at min

**REVIEWER'S COMMENTS:**

- The proposed dissolution methods is acceptable
- The proposed dissolution specification of at least % in min is not acceptable. It is recommended that the dissolution specification should be changed to *not less than* % at min (i.e.  $Q =$  % in min) for valsartan.
- The dissolution data provided to support the request for a bio-waiver for the 80 and 160 mg valsartan tablets is acceptable.

/s/

/s/

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Emmanuel Fadiran  
3/23/01 12:43:41 PM  
BIOPHARMACEUTICS

/s/

Angelica Dorantes  
3/26/01 03:44:03 PM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-283**

**Administrative Documents**

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Time Sensitive Patent Information  
Pursuant to 21 C.F.R. 314.53  
for  
NDA 21-283

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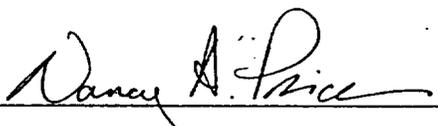
The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Diovan®  
Active Ingredient: Valsartan  
Strengths: 80 mg, 160 mg, 320 mg  
Dosage form: Tablets

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U.S. Patent Number: U.S. 5,399,578  
Expiration Date: March 21, 2012  
Type of Patent: Drug, Drug Product and Method of Use  
Name of Patent Owner: Novartis Pharmaceuticals Corporation

The undersigned declares that the above U.S. Patent number 5,399,578 covers the pharmaceutical composition of Diovan® (valsartan). This product is the subject of this application.

Signed  Date 7/25/00  
Nancy A. Price  
Associate Director  
Drug Regulatory Affairs

EXCLUSIVITY SUMMARY FOR NDA # 21-283

SUPPL # \_\_\_\_\_

Trade Name: Diovan      Generic Name: Valsartan Tablets

Applicant Name: Novartis Pharmaceuticals Corp.

HFD # 110

Approval Date If Known:

**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 question about the submission.

a) Is it an original NDA?

YES      / X / NO / \_\_\_ /

b) Is it an effectiveness supplement?

YES / \_\_\_ / NO / X /

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 / X /

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.

This NDA is for a change from the capsule formulation to the tablet formulation and required only review of chemistry data and 2 bioequivalence studies.

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 10/13/98

cc: Original NDA      Division File      HFD-93 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?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

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? (Rx to OTC switches should be answered NO-please indicate as such)

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# Diovan (valsartan) Capsules    NDA 20-665

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.

(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:

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(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      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:

\_\_\_\_\_  
\_\_\_\_\_

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                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

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

\_\_\_\_\_  
\_\_\_\_\_

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"):

\_\_\_\_\_  
\_\_\_\_\_

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: \_\_\_\_\_

\_\_\_\_\_

Signature   *S/*                        Date   7-3-01    
Title:   Project Manager

Signature of Office   *S/*                        Date   7/17/01    
Division Director

cc: Original NDA      Division File      HFD-93 Mary Ann Holovac

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

**PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)**

[View as Word Document](#)

**NDA Number:** 021283    **Trade Name:** DIOVAN (VALSARTAN) 80/160/320MG TABLETS  
**Supplement Number:** 000    **Generic Name:** VALSARTAN  
**Supplement Type:** N    **Dosage Form:**  
**Regulatory Action:** AE    **COMIS Indication:** HYPERTENSION  
**Action Date:** 6/8/01

**Indication # 1**    hypertension  
**Label Adequacy:** Adequate for ALL pediatric age groups  
**Formulation Needed:** NO NEW FORMULATION is needed  
**Comments (if any):**

**Ranges for This Indication**

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	Adult	Deferred	12/19/04

**Comments:** The firm will be conducting studies in response to a Pediatric Written Request issued December 19, 2000 that will be completed December 19, 2004. In a June 11, 2001 submission, the firm requested deferral of pediatric studies on the basis that adult studies are completed and ready for approval. The June 11, 2001 submission also included the status report of their pediatric drug development plans. Per Dr. Stockbridge, the requirement for pediatric studies can be deferred until December 19, 2004.

**This page was last edited on 7/17/01**

Signature

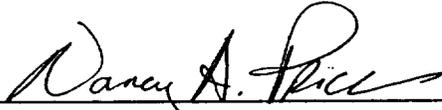
*LS*

Date

*7-17-01*

## DEBARMENT CERTIFICATION

NOVARTIS PHARMACEUTICALS CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act, in connection with this application.

Signed 

Date 6/13/2001

Nancy A. Price  
Associate Director  
Drug Regulatory Affairs

## **RHPM Labeling Review**

Application: NDA 21-283  
Diovan (valsartan) 80, 160, and 320 mg Tablets

Applicant: Novartis Pharmaceuticals Corporation

**Background:** An approvable letter was issued for NDA 21-283 on June 8, 2001. At that time, the following issues still had to be resolved:

Final printed labeling (including the actual carton and container labeling for Diovan 160 mg tablet samples) should be submitted.

*Resolution:* Novartis submitted the final printed labeling (package insert and immediate container and carton labels) in a submission dated June 18, 2001. This labeling is in accordance with the agreed upon submitted draft labeling, with the following exception:

- Under **HOW SUPPLIED** in the package insert, the 30 and 90 count bottles listing and corresponding NDC codes for all three dosage strengths have been deleted. Novartis noted the deletion because they do not plan to market the 30 and 90 count bottles at launch. The firm, however, failed to remove reference to these package sizes in the second sentence under **HOW SUPPLIED** in the package insert. In a July 17, 2001 telephone conversation between Ms. Nancy Price of Novartis Pharmaceuticals and Dr. Quynh Nguyen, Ms. Price agreed that the phrase "30 tablets, 90 tablets, or" would be removed from the second sentence under **HOW SUPPLIED** in the package insert at the time of the next printing. The sponsor's agreement to make this change will be noted in the approval letter.
- The draft labeling included both pressure sensitive and thermoplastic physician sample labels of 7-count tablets for all three dosage strengths, but the final printed labeling did not include the thermoplastic labels. Per Dr. Srinivasachar, this was acceptable since the draft labeling of the pressure sensitive and thermoplastic labels are identical, except for the label code numbers.

The application will be approved on the final printed labeling submitted.

The applicant was reminded of the approved specifications for both drug product and drug substance impurities and dissolution. They were asked to provide revised documents by July 15, 2001 for their approved specifications.

*Resolution:* Novartis had agreed to the approved specifications and to provide the revised documents for the approved specifications in their submission dated May 30, 2001. Ms. Catherine Ford of Novartis conveyed in a June 4, 2001 telephone message to Dr. Quynh Nguyen that the revised documents would be submitted by July 15, 2001. Novartis provided the revised documents in a submission dated July 9, 2001.

In a June 11, 2001 submission, the applicant requested deferral of pediatric studies on the basis that adult studies are completed and ready for approval. They plan to conduct pediatric studies and will submit data from these trials on or before December 19, 2004,

in agreement with a Written Request issued December 19, 2000. The June 11, 2001 submission also included the status report of their pediatric drug development plans.

*Resolution:* Per Dr. Stockbridge, the requirement for pediatric studies can be deferred until December 19, 2004.

**Comments/Recommendation**

There are no issues pending for this NDA. The approval letter will be drafted for approval based on final printed labeling for Dr. Lipicky's signature.

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager

7/17/01

qn/6-28-01/7-3-01/7-17-01

CSO NDA Overview  
June 7, 2001

**NDA 21-283** Diovan (valsartan) 80, 160, 320 mg Tablets

**Sponsor:** Novartis Pharmaceuticals Corporation

**Classification:** 3S

**Date of Application:** August 7, 2000

**Date of Receipt:** August 8, 2000

**User Fee Goal Date:** June 8, 2001

**Background**

Novartis Pharmaceuticals Corporation has submitted this original NDA for a new formulation of Diovan (valsartan) for the treatment of hypertension. Under NDA 20-665 approved December 23, 1996, Diovan is currently available as a capsule dosage form. Novartis is seeking approval of a tablet formulation, which the company believes would enhance both "patient acceptance and the production process." This NDA for the tablet formulation is being submitted as "no clinical data" for user fee purposes. Accordingly, this original NDA consists of chemistry, manufacturing and controls information and two bioequivalence studies to support approval of the new formulation. The submission refers to NDA 20-665 for non-clinical pharmacology, toxicology and clinical data.

This submission includes a 320 mg strength that is not currently available in capsule form. Novartis notes that while the 320 mg strength was not available as a single capsule, the approved labeling states that valsartan may be used up to a daily dose of 320 mg. The submission refers to the previously approved NDA for clinical data supporting use of valsartan 320 mg.

**Review**

Biopharmaceutics:

Reviewer: Emmanuel O. Fadiran, Ph.D.

Labeling: Acceptable

Conclusion: Dissolution method is acceptable, but asked the sponsor to change the dissolution specification (see Dr. Fadiran's 3-26-01 review). This recommendation was included in the action letter.

Chemistry:

Reviewer: Stuart Zimmerman, Ph.D.

Labeling: Acceptable

cGMP inspection: Acceptable, 5-30-01

Methods validation: To be initiated

Environmental Assessment: Acceptable. A FONSI was signed.

Review: Asked the sponsor to change the release and stability specification limits for impurities for both the drug substance and the drug product, to adopt an LOD specification limit of NMT 0.1% for both release and shelf-life testing, to send in revised Novartis Monograph control documents, Method of Preparation and Flow

Sheet of Manufacture documents. These recommendations were included in the action letter. Also asked sponsor to withdraw equivalency protocols dealing with the use of alternate suppliers and resubmit after NDA approval (see Dr. Zimmerman's 6-1-01 and two 5-31-01 reviews).

Patent info: Included in package

Pediatric info: The sponsor plans to submit a letter requesting deferral of the Pediatric Rule until December 19, 2004.  
Written Request issued on December 19, 2000. Status report of pediatric drug development plan will be submitted.

DSI: Not needed (formulation change)

Debarment Certification: Included in package

OPDRA Trade Name Review: OPDRA said: "We do not need to review the original name when there is a formulation change. We do still want to do a review of the carton/container label for safety issues."  
3-29-01  
OPDRA's 5-7-01 review of the carton/container labeling contained the following recommendations which were implemented by the sponsor: (1) The sponsor should differentiate its label between the 3 strengths to help in selecting the correct product since currently all 3 label strengths are in red ink; (2) The 160 mg sample label should be revised because it is difficult to read the label against the red background.

Quynh Nguyen, Pharm.D.

7/18/01

66 pages redacted from this section of  
the approval package consisted of draft labeling

## FILING SUMMARY

OCT 3 2000

NDA Number: NDA 21-283  
Drug Name: DIOVAN (valsartan) Tablets  
Indication: Treatment of hypertension  
Sponsor: Novartis Pharmaceuticals Corporation  
Therapeutic Classification: 3S  
Date of Application: 07 August 2000  
Date of Receipt: 08 August 2000  
User Fee Goal: 08 June 2001  
User Fee Status: Paid: 21 July 2000

**Submission Complete As Required Under 21 CFR 314.50? YES**

Patent Information Included? YES

Exclusivity Requested? NO

Debarment Statement Included? YES

**Pediatric Exclusivity:** Novartis intends to pursue pediatric exclusivity. They requested a formal Written Request. Letter drafted, with PdiT for comments.

### **BACKGROUND:**

Diovan was approved on 23 December 1996 as a capsule formulation for the treatment of hypertension. Novartis asserts the proposed tablet formulation would enhance both "patient acceptance and the production process. This NDA for the tablet formulation is being submitted as "no clinical data" for user fee purposes." As such it only includes chemistry, manufacturing and controls information and two bioequivalence studies to support approval of the new formulation. It refers to the previously approved NDA for the non-clinical pharmacology, toxicology and clinical data.

The submission includes a 320 mg strength that is not currently available in capsule form. The firm notes that approved labeling refers to the use of valsartan of up to 320 mg daily.

Tuesday, September 26, 2000

**ASSIGNED REVIEWERS:**

DISCIPLINE	REVIEWER
Medical:	Norman Stockbridge, MD
Sec. Medical:	Norman Stockbridge, MD
Pharmacology:	Charles Resnick, Ph.D.
Chemist:	Stuart E. Zimmerman, Ph. D.
Biopharmaceuticist:	Nhi Nguyen, Ph. D.
Project Manager:	Natalia A. Morgenstern, Chief Project Management Staff

**CHEMISTRY -**

Did firm request categorical exclusion for environmental assessment?    YES

EIR package transmitted?    YES, 26 September 2000

Trade Name Review Requested?    Not needed, no plans to change trade name.

**MEETING:**

No meeting was held. Only two reviews are required for this "no clinical data" NDA: biopharmaceutics and chemistry. Both Drs. Nguyen and Zimmerman have no filing issues. The NDA therefore will be filed on 7 October 2000.

*ISI*  
/ Natalia A. Morgenstern  
Chief, Project Management Staff, HFD-110

cc:  
Orig. NDA  
HFD-110  
HFD-110/ABlount  
HFD-110/NNguyen  
HFD- 110/SZimmerman

Tuesday, September 26, 2000

Methods Validation:

Per Dr. Zimmerman's 6-1-01 review, the Methods Validation is to be initiated shortly.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** 04/05/01

**DUE DATE:** 05/2/01

**OPDRA CONSULT #:** 01-0080

**TO:**

Raymond Lipicky, MD  
Director, Division Cardio-Renal Drug Products  
HFD-110

**THROUGH:**

Quynh Nguyen  
Project Manager  
HFD-110

**PRODUCT NAME:**

Diovan (valsartan) Tablets: 80 mg, 120 mg, 360 mg.

**NDA:** 21-283

**MANUFACTURER:** Novartis Pharmaceuticals Corp.

**SAFETY EVALUATOR:** David Diwa, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA has performed a review of the proposed product container labels and carton labeling of Diovan to determine safety issues relating to potential medication errors.

**OPDRA RECOMMENDATION:**

OPDRA recommends implementation of labeling revisions to minimize potential user error.

*/S/*

*/S/*

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 05/01/01  
NDA: 21-283  
NAME OF DRUG: Diovan (valsartan) Tablets  
NDA HOLDER: Novartis Pharmaceuticals Corporation

**I. INTRODUCTION:**

This consult is written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) for an assessment of the proposed product container label and carton labeling for Diovan.

PRODUCT INFORMATION

Diovan (valsartan) is an angiotensin II receptor antagonist used alone or in combination with other antihypertensives in the treatment of hypertension. The sponsor has submitted proposed labeling for oral tablet formulation in strengths of 80 mg, 160 mg and 320 mg. Currently, valsartan is available as Diovan HCT in capsule formulations of 80 mg and 160 mg.

**II. LABELING, PACKAGING AND SAFETY RELATED ISSUES**

In the review of the container label and carton labeling for Diovan, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement for both the container label and carton labeling, which might minimize potential user error.

1. We would recommend that the sponsor differentiate its label between the 3 strengths. This will help in selecting the correct product. Currently, all 3 label strengths are in red ink.
2. It is difficult to read the label against the red background on the 160 mg sample label.  
- Please revise.

**APPEARS THIS WAY  
ON ORIGINAL**

**III. RECOMMENDATIONS:**

OPDRA recommends implementation of the above labeling revisions to minimize potential user error.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact David Diwa at 301-827-0892.

**/S/**

---

David Diwa, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

**/S/**

---

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

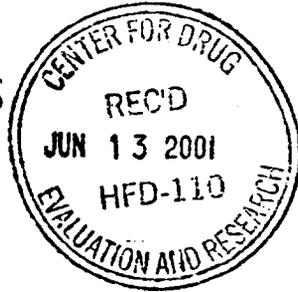
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-283**

**Correspondence**

 NOVARTIS



Novartis Pharmaceuticals Corporation  
Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Tel 973 781 7500  
Fax 973 781 3590

Raymond Lipicky, MD  
Director  
Division of Cardio-Renal Drug Products  
HFD-110  
Office of Drug Evaluation I  
Attn: Document Control Room  
Center for Drug Evaluation and Research  
5600 Fishers Lane  
Rockville, Maryland 20857

June 11, 2001

NDA No. 21-283  
Diovan® (valsartan) Tablets

Pediatric Study Requirement  
Status Report  
Deferral Request

Dear Dr. Lipicky:

Reference is made to a verbal request we received on June 5, 2001 for an update on the status of our pediatric study initiatives involving Diovan (valsartan).

As you know, your Division issued a Written Request on December 19, 2000 which pertained to both NDA 21-283 (Diovan tablets) and NDA 20-665 (Diovan capsules). Four trial options for the dose ranging study were identified in your letter, and in the intervening months we have been conferring with pediatric specialists as well as contract research organizations to identify the most appropriate option to pursue. We will communicate with you in the near future concerning our preferred option. As of this time we have not initiated a study, and as a consequence no patients have been enrolled.

We are requesting a deferral of pediatric studies as adult studies are completed and ready for approval. Please find attached our deferral request, which is formatted as per the draft guidance *Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))*, dated November 2000. As mentioned above, we are making plans to conduct these studies and will submit data from these trials on or before December 19, 2004, in agreement with our Written Request.

If you have any questions or comments concerning this matter, please contact me at (973) 781-3591 (phone) or (973) 781-3590 (FAX).

Sincerely,

Nancy A. Price  
Associate Director  
Drug Regulatory Affairs

Attachment  
NAP/kp  
Submitted in duplicate

Desk copy, via fax: Dr. Quynh Nguyen, Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: March 31, 2003  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT <b>NOVARTIS PHARMACEUTICALS CORPORATION</b>	DATE OF SUBMISSION June 11, 2001
TELEPHONE NO. (Include Area Code) (973) 781-3591	FACSIMILE (FAX) Number (Include Area Code) (973) 781-3590
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):  59 Route 10 East Hanover, New Jersey 07936-1080	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) <b>21-283</b>		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) <b>Valsartan</b>	PROPRIETARY NAME (trade name) IF ANY <b>Diovan®</b>	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any) <b>CGP 48933</b>	
DOSAGE FORM: <b>Tablets</b>	STRENGTHS: <b>80 mg; 160 mg; 320 mg</b>	ROUTE OF ADMINISTRATION: <b>Oral</b>
(PROPOSED) INDICATION(S) FOR USE: <b>Hypertension</b>		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION PEDIATRIC STUDY REQUIREMENT: STATUS REPORT AND DEFERRAL REQUEST
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1. Index	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
2. Labeling (check one)		
3. Summary (21 CFR 314.50 (c))		
4. Chemistry section		
A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)		
B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)		
5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)		
6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)		
7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))		
8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)		
9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)		
10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)		
11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)		
12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)		
13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))		
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))		
15. Establishment description (21 CFR Part 600, if applicable)		
16. Debarment certification (FD&C Act 306 (k)(1))		
17. Field copy certification (21 CFR 314.50 (k)(3))		
18. User Fee Cover Sheet (Form FDA 3397)		
19. Financial Information (21 CFR Part 54)		
20. OTHER (Specify)		

**CERTIFICATION**

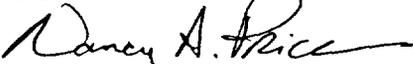
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Nancy A. Price, Associate Director Drug Regulatory Affairs	DATE 6/11/2001
---	---	-------------------

ADDRESS (Street, City, State, and ZIP Code) 59 Route 10 East Hanover, New Jersey 07936-1080	Telephone Number (973) 781-3591
---	------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--

## REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

**IND/NDA/BLA number:** NDA 21-283  
**Sponsor:** Novartis Pharmaceuticals  
**Indications(s):** Hypertension  
**Product:** Diovan (valsartan) tablets

(a) Is the indication for a life-threatening condition that occurs in the pediatric population?

Yes \_\_\_ No X

(b) If yes, are there approved therapies labeled for use in the pediatric population?

Yes \_\_\_ No \_\_\_\_\_

(c) If yes, list the approved therapies and labeled pediatric age group(s) of approval.

1. What ages are included in your deferral request? All

Reason for not including the entire pediatric population in the studies or in the deferral request: Not applicable

(a) Adequate pediatric labeling

(b) Studies completed in ages

(c) Requesting a waiver

(d) Other

(e) Currently conducting pediatric studies that will be submitted with application

2. Reason(s) for deferring pediatric studies:

(a) Adult studies completed and ready for approval X

(b) Additional postmarketing safety data needed \_\_\_\_\_

(c) Technological problems with development of a pediatric formulation  
(provide documentation) \_\_\_\_\_

(d) Difficulty in enrolling pediatric patients (provide documentation)

(e) Other (specify)

3. Have pediatric drug development plans been submitted to the Agency?

Yes \_\_\_\_\_ No X

If yes, date submitted:

If no, projected date pediatric plan is to be submitted: In June 2001 we plan to submit an inquiry on the design of the Pediatric dose ranging study.

4. Suggested deferred date for submission of studies

December 19, 2004, in agreement with the Written Request

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

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**Transmitted to FAX Number:** (973) 781-3590

**Attention:** Ms. Nancy Price

**Company Name:** Novartis Pharmaceuticals Corp.

**Phone:** (973) 781-3591

**Subject:** **Comment regarding Clinical Pharmacology and Biopharmaceutics**

**Date:** April 2, 2001

**Pages including this sheet:** 2

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** (301) 594-5311  
**Fax:** (301) 594-5494

Dear Nancy,

Please find attached a comment from Dr. Fadiran, Clinical Pharmacologist and Biopharmaceutist, regarding NDA 21-283. If you have any questions, please feel free to contact me at the above numbers.

Thanks,  
Quynh

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

**COMMENT TO BE SENT TO THE SPONSOR:**

DISSOLUTION: The proposed dissolution specification of at least  $\frac{1}{2}$  % in  $\frac{1}{2}$  min is not acceptable. Based on the dissolution data submitted to the NDA it is recommended that the dissolution specification should be changed to *not less than*  $\frac{1}{2}$  % at  $\frac{1}{2}$  min (i.e. Q =  $\frac{1}{2}$  % in  $\frac{1}{2}$  min) for valsartan.

APPEARS THIS WAY  
ON ORIGINAL

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ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

AUG 23 2000

NDA 21-283

Novartis Pharmaceuticals Corporation  
Attention: Ms. Nancy A. Price  
59 Route 10  
East Hanover, NJ 07936-1080

Dear Ms. Price:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Diovan (valsartan) 80, 160, 320 mg

Review Priority Classification: Standard (S)

Date of Application: August 7, 2000

Date of Receipt: August 8, 2000

Our Reference Number: NDA 21-283

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 7, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 8, 2000 and the secondary user fee goal date will be August 8, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products,  
HFD-110  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products,  
HFD-110  
Attention: Division Document Room  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

NDA 21-283

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If you have any questions, please call me at 301-594-5300.

Sincerely,

/s/

Natalia A. Morgenstern  
Chief, Project Management Staff  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research