CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-283/S011

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

Brand name:	Diovan
Generic name:	Valsartan
Dosage form and strengths:	new 40 (scored), 80, 160, 320 mg tablets
Indication:	post myocardial infarction
NDA:	21-283
Reference number:	011
Type:	efficacy supplement, SE1
Applicant:	Novartis
Submission dates:	December 17, 2003 February 20, 2004 March 18, 2004
OCPB Division:	Pharmaceutical Evaluation I
OND Division:	Cardio-Renal Drug Products
Reviewer:	B. Nhi Beasley, Pharm.D.
Team Leader:	Patrick Marroum, Ph.D.

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1. Executive Summary

Novartis is seeking the approval of valsartan in the early and long-term treatment of post MI patients with heart failure or left ventricular dysfunction to improve survival and reduce cardiovascular mortality and morbidity. Valsartan is an orally active angiotensin II type I blocker (ARB) indicated for hypertension and heart failure. The decision of approval will be

based on the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial in 14,703 patients worldwide. The primary endpoint was all-cause mortality. The study evaluated valsartan alone, an ACE inhibitor (captopril) alone, and valsartan in combination with captopril. Valsartan monotherapy was titrated as follows: 20 mg bid, 40 mg bid, 80 mg bid followed by 160 mg bid. Titration was based on systolic blood pressure (SBP), symptoms of hypotension, and serum creatinine values.

Because the initial dose post-MI in VALIANT was 20 mg bid, and the lowest marketed strength is a 40 mg unscored tablet, the sponsor has proposed to replace the current round, film-coated 40 mg tablet with an ovaloid, scored, film-coated 40 mg tablet. The approval of the new ovaloid scored 40 mg tablet is based only on in-vitro dissolution data in the approved medium, because the tablet formulations are identical except for the shape, the score and the addition of a ——— non-functional film-coat. The two tablets have similar dissolution profiles in pH 6.8. Thus, a waiver from doing a bioequivalence study for the new 40 mg tablet can be granted, and the new tablet can replace the currently marketed tablet.

With regard to obtaining the 20 mg dose from one-half of the 40 mg dose, a 20 mg capsule was used in VALIANT, instead of one-half of the currently marketed 40 mg tablet (the formulation that the biowaver is based upon). The 20 mg capsule ——————————— to any of the 40 mg formulations. Thus, a waiver cannot be granted for the 20 mg dose, however only about 10 % of patients randomized to the valsartan arms were on the 20 mg dose at the final visit (last observation carried forward, primary analysis population) since the doses in VALIANT were titrated up. The mean daily dose of valsartan in the valsartan only arm was 217 mg.

1.1 Recommendations

The new ovaloid, scored, film-coated 40 mg tablet is bioequivalent to the current round, film-coated 40 mg tablet. The current and the new 40 mg tablets are interchangeable. Breaking the scored 40 mg tablet in half to obtain 20 mg is reasonable given that the treatment is titrated up to 160 mg b.i.d.

1.2 Phase IV Commitments

N/A

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor intends to replace the lowest valsartan strength, a round, film-coated 40 mg tablet with an ovaloid, scored, film-coated 40 mg tablet because the proposed initial dose in post-MI patients is 20 mg. A 20 mg capsule formulation was used in the post-MI trial, VALIANT. Thus, exemption from a bioequivalence study for the 20 mg formulation, a biowaiver, requires that the sponsor show that

1. The formulation used in the clinical trial is proportionally similar to the to-be-marketed formulation.
2. Comparative dissolution profiles in at least three media are similar for the 20 mg capsule and one-half the ovaloid scored 40 mg tablet.

3. Since the biowaiver is a downward waiver, i.e, use of data from the 40 mg tablet to obtain approval of a lower strength, dose proportionality is unimportant.

The 20 mg capsule used in VALIANT [redacted] the current 40 mg tablet. The composition of the 20 mg capsule (in VALIANT) and the current 40 mg tablet are shown in Table 1 for comparison.

Table 1. Comparison of 20 mg and 40 mg capsules used in VALIANT and 40 mg to-be-marketed tablet

Ingredient	20 mg capsule	40 mg to-be-marketed and current tablet
Tablet core	**mg**	**Mg**
Valsartan	20.0	40.0
[redacted]	[redacted]	[redacted]
Magnesim stearate	[redacted]	[redacted]
Crospovidone	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Microcrystalline cellulose	[redacted]	[redacted]
Colloidal silicon dioxide	[redacted]	[redacted]
Core weight	[redacted]	[redacted]
Total mass of filled capsule/tablet	[redacted]	[redacted]

Thus, a biowaiver cannot be granted for the 20 mg dose, however, 20 mg was the initial starting dose, and patients were titrated up to 160 mg b.i.d. Few patients were taking 20 mg b.i.d. at the end of the trial. Therefore, no link between the 20 mg capsule used in the clinical trial and the to-be-marketed formulation is necessary since no data using this formulation was used for decision making.

The 40 mg capsule used in VALIANT has been deemed bioequivalent to the currently marketed 40 mg tablet (biowaiver granted in 2001). Approval of the new 40 mg ovaloid tablet to replace the current 40 mg tablet only requires dissolution data in the approved medium, pH 6.8. The dissolution profiles of the currently marketed 40 mg round, film-coated tablet, a whole ovaloid scored tablet and one half of the ovaloid scored tablet were similar.

The 80 mg capsule and 160 mg capsule was used in VALIANT. These capsules were marketed in the past and replaced with the respective bioequivalent tablet.

The sponsor submitted two clinical pharmacology studies that are irrelevant to the approval of the new ovaloid scored 40 mg tablet. These studies were relative bioavailability studies in healthy subjects. Study 2301 was an open-label, single-dose, three period, randomized, crossover study that investigated the relative bioavailability of two tablet formulations of 20 mg valsartan compared to 20 mg valsartan capsule. Study 2304 was an open-label, single dose, two-period, randomized, crossover study that investigated the relative bioavailability of 4 x 10 mg valsartan tablets (CSF) compared to a 40 mg valsartan tablet. Both studies are not useful for the

approval of the 40 mg tablet since they describe the relative bioavailability of several formulations that the sponsor is not marketing. Thus, neither study was reviewed.

The current dissolution specifications and methodology will also apply to the new tablet.

Apparatus: paddle
Media: p.H. 6.8 (0.067 M phosphate buffer)
Volume (mL) 1000 mL
Speed: 50 rpm
Specification: [redacted]

B. Nhi Beasley, Pharm.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D.
CC list: HFD-110: NDA 21-283; HFD-860: (Mehta, Rahman); CDER Central Document Room

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2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What is the proposed therapeutic indication?

Novartis is seeking the approval of valsartan in the early and long-term treatment of post MI patients with heart failure or left ventricular dysfunction to improve survival and reduce cardiovascular mortality and morbidity.

2.2 General Clinical Pharmacology

N/A

2.3 Intrinsic Factors

N/A

2.4 Extrinsic Factors

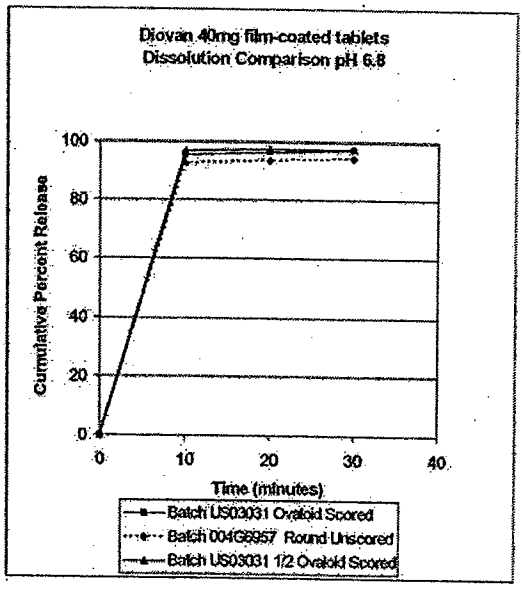
N/A

2.5 General Biopharmaceutics

2.5.1 Should a waiver for the 40 mg ovaloid scored tablet be granted?

Yes, a biowaiver should be granted for the 40 mg ovaloid scored tablet. The two tablets are identical in formulation except for the shape, score and the addition of a ——— non-functional film-coat. Only dissolution profiles in the approved medium are required. The dissolution profiles in the approved medium, ——————— for the currently marketed 40 mg round, film-coated tablet, a whole ovaloid scored tablet and one half of the ovaloid scored tablet are similar (figure below).

Figure 1 Diovan 40mg, dissolution media pH 6.8



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Individual dissolution data can be found in the individual study review (page 32). It is noted that 12 ovaloid tablets (whole and half portion) were used, but only six currently marketed tablets tablets were used. (See table that follows.)

Table A5 Drug Product Dissolution Testing

Date of test	Dosage form and strength	Lot No:	Dissolution apparatus	Media, temperature (°C)	Speed of rotation (r.p.m)	Units Tested	Collection time (min)	Mean % Dissolved
9/14/2003	40 mg divisible tab	US03031	Paddle (USP)	pH 6.8, 37 °C	50 rpm	12	10, 20, 30	95.5, 96.6, 97.2
4/21/2003	40 mg fct*	004G6957				6		92.6, 93.8, 94.3
9/14/2003	Half-of 40 mg divisible tab**	US03031				12 (from 6 tablets)		96.7, 97.4, 97.6

The similarity factors ranged between 50 to 100, indicating the similar dissolution profiles (see table below).

Tablet Comparison	Buffer pH 6.8
Ovaloid scored vs. Half ovaloid scored	94.09
Ovaloid scored vs. Round unscored	75.93
Half ovaloid scored vs. Round unscored	71.03

2.5.2 Can the 20 mg dose used in VALIANT be obtained from the new 40 mg ovaloid scored tablet?

It is not known if using one-half of the 40 mg scored ovaloid tablet is bioequivalent to the 20 mg capsule used in VALIANT.

A 20 mg capsule formulation was used in the post-MI trial, VALIANT. Thus, exemption from a bioequivalence study for the 20 mg formulation, a biowaiver, requires that the sponsor show that

1. The formulation used in the clinical trial is proportionally similar to the to-be-marketed formulation.
2. Comparative dissolution profiles in at least three media are similar for the 20 mg capsule and one-half the ovaloid scored 40 mg tablet.

The 20 mg capsule used in VALIANT is not proportionally similar to the current 40 mg tablet. The composition of the 20 mg capsule (in VALIANT) and the current 40 mg tablet are shown in Table 2 for comparison.

Table 2. Comparison of 20 mg and 40 mg capsules used in VALIANT and 40 mg to-be-marketed tablet

Ingredient	20 mg capsule	40 mg to-be-marketed and current tablet
Tablet core	**mg**	**Mg**
Valsartan	20.0	40.0
[redacted]	[redacted]	[redacted]
Magnesim stearate	[redacted]	[redacted]
Crospovidone	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Microcrystalline cellulose	[redacted]	[redacted]
Colloidal silicon dioxide	[redacted]	[redacted]
Core weight	[redacted]	[redacted]
Total mass of filled capsule/tablet	[redacted]	[redacted]

Thus, a biowaiver cannot be granted for the 20 mg dose, however, the 20 mg was the initial starting dose, and patients were titrated up to 160 mg b.i.d. Few patients were taking 20 mg b.i.d. at the end of the trial. Therefore, no link between the 20 mg capsule used in the clinical trial and the to-be-marketed formulation is necessary since no data using this formulation was used for decision making.

2.6 Analytical Section

N/A

3. Detailed Labeling Recommendations

There are no labeling recommendations.

31 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling