CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-818/S-016

Medical Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 20-818 (valsartan/HCTZ)

Sponsor: Novartis

Submission: SE8-002 (11 April 2002): a request to amend the recommended dosage and administration instructions to reflect the current starting dose instructions for valsartan monotherapy.

Review date: September 23, 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

As a result of an approved labeling supplement to NDA 21-283, valsartan can be initiated at 80 or 160 mg once daily. The current supplement is intended to update accordingly the label for valsartan-HCTZ.

The sponsor's proposed changes are confined to the DOSAGE AND ADMINISTRATION section. The proposed initial paragraph now reads in part:

> *The recommended starting dose of valsartan is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume depleted. Patients requiring greater reductions may be started at the higher dose....*

This is entirely consistent with approved labeling for valsartan monotherapy.

This change is propagated into the proposed into the dose titration instructions as follows:

> ***Dose titration by Clinical Effect:*** *Diovan HCT tablets contain valsartan and hydrochlorothiazide 80/12.5 mg, 160/12.5 mg and 160/25 mg. A patient whose blood pressure is not adequately controlled with valsartan monotherapy (see above) may add hydrochlorothiazide by switching to Diovan HCT (valsartan 80 mg/hydrochlorothiazide 12.5 mg or valsartan 160 mg/hydrochlorothiazide 12.5 mg) once daily....*

Similar instructions follow for switching patients inadequately controlled on HCTZ alone.

While it does not necessarily follow that that instructions for initiation of valsartan alone lead to the same instructions for migration to valsartan-HCTZ, in this case, the label does not even distinguish the magnitude of blood pressure effects of the 80/12.5 and 160/12.5 combinations. Consequently, the sponsor's proposed changes should be approved.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 21-283

Sponsor: Novartis

Submission: SLR-002 (18 October 2001): a request to increase the starting dose from 80 to 160 mg for valsartan in the treatment of mild-to-moderate essential hypertension.

Review date: February 8, 2002

Reviewers: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-283

HFD-110/Project Manager

The sponsor proposes to make the usual starting dose in essential hypertension be 160 mg, rather than 80 mg, as currently labeled. The rationale offered is (1) greater blood pressure reduction has public health benefits, (2) achieving the target reduction in fewer visits is desirable, and (3) 160 mg is safe as a starting dose.

The sponsor has provided a summary of fixed-dose dose-response from a number of placebo-controlled studies. These data are shown in Figure 1.

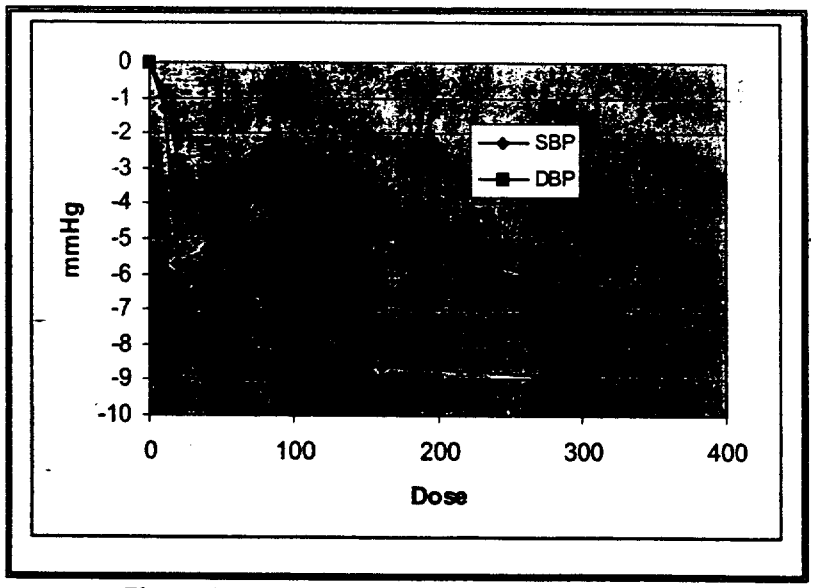

Figure 1. Raw mean dose-response for valsartan

Data from 9 randomized, double-blind, paralell, placebo-controlled studies of valsratan as reported by Pool et al. (1998) Clinical Therapeutics 20(6):1106-1114.

The mean difference in blood pressure between the 80 and 160 mg doses is -1.8/-1.2 mmHg[1].

The following table summarizes safety data from Dr. Ganley's primary medical review of valsartan (under NDA 20-665).

Table 55.7. Most Commonly Reported Adverse Events (> 1%) Based On Dose In Placebo Controlled Trials

Total Patients	25 (100)	385 (100)	427 (100)	1281 (100)	699 (100)	385 (100)	388 (100)
Patients with AE's	11 (44.0)	141 (36.6)	131 (31.0)	465 (36.3)	251 (35.9)	75 (40.3)	178 (45.9)
Adverse Experiences							
Headache	2 (8.0)	59 (30.1)	28 (6.6)	106 (8.3)	54 (8.2)	11 (5.9)	129 (15.9)
Dizziness	1 (4.0)	9 (2.3)	12 (2.8)	33 (2.6)	14 (2.1)	15 (8.1)	31 (3.5)
Infection Viral	0 (0.0)	11 (2.9)	7 (1.7)	34 (2.7)	18 (2.7)	3 (1.6)	17 (1.9)
URI	2 (8.0)	4 (1.0)	1 (0.2)	22 (1.7)	21 (3.2)	9 (4.9)	21 (2.4)
Coughing	1 (4.0)	6 (1.6)	5 (1.2)	21 (1.6)	15 (2.3)	6 (3.2)	13 (1.5)
Diarrhea	1 (4.0)	8 (2.1)	4 (0.9)	23 (1.8)	11 (1.7)	4 (2.2)	26 (3.0)
Fatigue	0 (0.0)	7 (1.8)	7 (1.7)	23 (1.8)	10 (1.5)	2 (1.1)	11 (1.2)
Rhinitis	0 (0.0)	6 (1.6)	4 (0.9)	25 (2.0)	9 (1.4)	3 (1.6)	20 (2.3)
Sinusitis	1 (4.0)	3 (0.8)	9 (2.1)	17 (1.3)	9 (1.4)	6 (3.2)	14 (1.6)
Pain Back	0 (0.0)	5 (1.3)	3 (0.7)	19 (1.5)	11 (1.7)	0 (0.0)	12 (1.4)
Pain Abdominal	0 (0.0)	5 (1.3)	5 (1.2)	16 (1.2)	6 (0.9)	4 (2.2)	9 (1.0)
Nausea	0 (0.0)	3 (0.8)	2 (0.5)	22 (1.7)	6 (0.9)	2 (1.1)	18 (2.0)
Pharyngitis	0 (0.0)	5 (1.3)	2 (0.5)	8 (0.6)	8 (1.2)	4 (2.2)	6 (0.7)
Arthralgia	0 (0.0)	2 (0.5)	2 (0.5)	14 (1.1)	5 (0.8)	1 (0.5)	9 (1.0)

Protocols included: 05, 46, 09, 10, 11 Cont. 17, 23, 31 Cont. 50 and 51

Headache and dizziness are perhaps increased at 320 mg, but there is not much suggestion of dose-related adverse effects below that dose.

Starting doses for other angiotensin receptor antagonists are shown in Table 1.

Table 1. Starting doses for various angiotensin receptor antagonists.

Drug	Start	Mean effect
Candesartan	16 mg	>8/4 mmHg
Irbesartan	150 mg	7/4 mmHg
Losartan	50 mg	6/4 mg
Telmesartan	40 mg	11/7 mg

With the proposed change, the mean effect of valsartan's starting dose would remain within the range of effect sizes seen with the starting doses of other angiotensin receptor antagonists.

The sponsor's proposed changes to the label are confined to the DOSAGE AND ADMINISTRATION section, as follows:

The recommended starting dose of Diovan is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. 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 over the starting dose range, the dose may be increased to a maximum of

[1] *Curiously, however, the publication concludes "In clinical practice, valsartan 80 mg once daily is an appropriate starting dosage for most hypertensive patients."*

320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

This supplement should be approved.

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/s/

Norman Stockbridge
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MEDICAL OFFICER