May 09, 2008

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Dear Dr. Citron:

Your Sales Representative, Stephanie Davis, has forwarded your inquiry concerning Avalide® (irbesartan-hydrochlorothiazide). You requested information regarding use of Avalide for the initial treatment of hypertension.

Avalide is indicated for the treatment of hypertension. Avalide may be used in patients whose blood pressure is not adequately controlled on monotherapy. Avalide may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Avalide as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

Initial Use in Severe Hypertension

Neutel et al conducted a prospective, randomized, double-blind, multicenter, 7-week study to compare Avalide combination therapy to irbesartan monotherapy in adult patients with untreated, uncontrolled hypertension (seated diastolic blood pressure [SeDBP] ≥110 mm Hg) or in those who were not controlled on antihypertensive monotherapy (SeDBP ≥100 mm Hg).[1] Following an approximately 7-day, single-blind placebo washout, subjects with SeDBP ≥110 mm Hg were randomized in a 2:1 ratio to Avalide 150/12.5 mg or irbesartan 150 mg, with a forced titration to 300/25 mg and 300 mg, respectively, at the end of Week 1. The total duration of treatment was 7 weeks. The primary endpoint was the proportion of subjects with a trough SeDBP <90 mm Hg at Week 5. Safety was evaluated and also included pre-specified adverse events (AEs) such as syncope, hypotension, dizziness, headache, hypokalemia, and hyperkalemia. Efficacy and safety assessments were made at Weeks 1, 3, 5, and 7.

A total of 697 patients (Avalide group, n=468 and irbesartan group, n=229) were randomized (mean age approximately 52 years [13% ≥65 years], 57.5% male, mean baseline blood pressure [BP] 172/113 mm Hg). The demographic characteristics were similar in both treatment groups (**Table 1**).

Table 1. Baseline Characteristics[1]

	Avalide (n=468)	Irbesartan Monotherapy (n=229)
Demographics		
Male/Female, n (%)	277/191 (59.2/40.8)	124/105 (54.1/45.9)
Race, n (%)		
Caucasian	395 (84.4)	192 (83.8)
Black/African American	67 (14.3)	34 (14.8)
Asian	3 (0.6)	2 (0.9)
Native Hawaiian/other Pacific Islander	1 (0.2)	0
Mean age (range), years	52.2 (23-81)	52.9 (25-83)
Mean weight (range), kg	89.7 (48.0-164.3)	91.8 (44.0-151.5)
Cardiovascular History		
Mean duration of hypertension (range), years	7.2 (0-48.9)	7.1 (0-35.8)
Mean SeDBP (range), mm Hg	113.4 (92.8-131.6)	113.3 (103.0-135.0)
Mean SeSBP (range), mm Hg	171.5 (132.3-221.7)	171.6 (134.7-220.7)
Diabetes mellitus, n (%)	52 (11.1)	30 (13.1)
Hyperlipidemia, n (%)	158 (33.8)	78 (34.1)
Stable angina pectoris, n (%)	12 (2.6)	12 (5.2)
Stroke or TIA, n (%)	6 (1.3)	7 (3.1)
Myocardial Infarction, n (%)	6 (1.3)	3 (1.3)

SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; TIA, transient ischemic attack

The percentage of subjects who achieved a trough SeDBP <90 mm Hg at Week 5 (primary endpoint) was significantly higher in the Avalide group (47.2%) compared to the irbesartan monotherapy group (33.2%; P=0.0005) (**Table 2**). The mean change in SeSBP from baseline was significantly greater with Avalide at each time point compared to irbesartan monotherapy (all P<0.0001). The mean change in SeDBP from baseline was also significantly greater with Avalide compared to irbesartan monotherapy, beginning at Week 1 (P=0.0006), and at Weeks 3, 5, and 7 (all P<0.0001). By Week 7, SeSBP decreased by a mean of 31.7 mm Hg and SeDBP decreased by a mean of 24.5 mm Hg from baseline in the Avalide group. Avalide treatment resulted in mean SeSBP and SeDBP reductions of 27 and >20 mm Hg, respectively, by Week 3, while comparable decreases with irbesartan monotherapy were not achieved until Week 7. During Weeks 3-7, more patients in the Avalide group had a SeDBP <90 mm Hg compared to irbesartan monotherapy (14-19% greater than monotherapy, P<0.0001 at each time point). More patients in the Avalide group achieved SeSBP/SeDBP <140/90 mm Hg compared to the irbesartan monotherapy group at Weeks 1, 3, 5, and 7.

Table 2. Efficacy Results[1-3]

		Avalide (n=468)	Irbesartan Monotherapy (n=229)	Estimated Difference Between Treatments	*P*-value[a]
Primary Endpoint					
Controlled SeDBP[b], %	Week 5	47.2	33.2	14.0	0.0005
Secondary Endpoints					
Mean change in SeSBP/SeDBP, mm Hg	Week 5	-30.8/-24.0	-21.1/-19.3	-9.7/-4.7	<0.0001
SeDBP <90 mm Hg, %	Week 1	15.2	9.2	6.0	0.03
	Week 7	51.9	32.8	19.1	<0.0001
Controlled SeBP[c], %	Week 1	9.2	4.4	4.8	0.023
	Week 3	30.6	12.7	17.9	<0.001
	Week 5	34.6	19.2	15.4	<0.0001
	Week 7	37.8	21.4	16.4	<0.0001
Severe hypertension[d], %	Week 5	5.4	13.8	8.4	0.0003

[a]*P*-value for between group comparison
[b]Trough SeDBP <90 mm Hg
[c]Trough SeDBP <90 mm Hg and trough SeSBP <140 mm Hg
[d]Severe hypertension defined as BP ≥180/110 mm Hg

The overall frequency of AEs was lower with combination therapy compared to monotherapy (29.9% versus 36.1%, respectively). Safety results are provided in **Table 3**. Most of the AEs were mild-to-moderate in intensity. In both groups, there were fewer AEs reported by patients ≥65 years compared to patients <65 years of age. Nine (1.9%) and 5 patients (2.2%) discontinued treatment due to AEs in the Avalide and irbesartan groups, respectively. Of these, 3 in the Avalide group were considered treatment-related (dizziness, fatigue, and hypertension), and the remainder were not considered related to study medication. The rate of pre-specified AEs was lower in the Avalide group compared with the irbesartan monotherapy group. Syncope was not reported in either group. There was one serious AE reported in each group; both were determined to be unrelated to study drug and did not require treatment discontinuation. No deaths occurred during the study.

Table 3. Safety Results at Week 7[1]

	Avalide (n=468)	Irbesartan Monotherapy (n=229)
Adverse Events, n (%)		
Overall	140 (29.9)	82 (36.1)
≥65 years old[a]	N/A (26.4)	N/A (34.2)
<65 years old	N/A (30.4)	N/A (36.5)
Pre-specified AEs, n (%)	41 (8.8)	26 (11.5)
Dizziness	17 (3.6)	9 (4.0)
Headache	20 (4.3)	15 (6.6)
Hyperkalemia	1 (0.2)	0
Hypokalemia	3 (0.6)	1 (0.4)
Hypotension	3 (0.6)	0
Serum potassium <3.0 mmol/L	0	0
Serum potassium >6.0 mmol/L	3 (0.6)	3 (1.3)
Serious AEs, n (%)	1 (0.2)	1 (0.4)
Discontinuations due to AEs, n (%)	9 (1.9)	5 (2.2)

N/A = not available
[a] n=92

The authors concluded that Avalide therapy used as initial treatment for patients with severe hypertension decreased BP more rapidly and to a greater extent, and had comparable safety to irbesartan monotherapy.

Initial Use in Moderate Hypertension

Neutel et al conducted a prospective, multicenter, randomized, double-blind, 12 week study to compare Avalide combination therapy to irbesartan monotherapy and hydrochlorothiazide (HCTZ) monotherapy in patients with moderate hypertension.[4] Patients who were untreated with moderate hypertension (SeSBP 160-179 mm Hg or SeDBP 100-109 mm Hg) or patients on monotherapy (treatment with a single antihypertensive agent for ≥ 4 weeks) with SeSBP 150-179 mm Hg or SeDBP 95-109 mm Hg were eligible for enrollment. Patients who had severe hypertension defined as SeSBP ≥ 180 or SeDBP ≥ 110 mm Hg were excluded. Following a 21-day placebo washout, eligible patients were randomized in a 3:1:1 ratio to Avalide 150/12.5 mg, irbesartan 150 mg, or HCTZ 12.5 mg, with a forced titration to Avalide 300/25 mg, irbesartan 300 mg, and HCTZ 25 mg, respectively, at Week 2. The total duration of treatment was 12 weeks. The primary endpoint was the change from baseline in SeSBP at Week 8. Safety was evaluated and also included the frequency of pre-specified AEs such as hypotension, dizziness, syncope, headache, hypokalemia, and hyperkalemia. Patients were assessed at Weeks 2, 4, 8, and 12.

A total of 538 patients were randomized. The demographic and clinical characteristics were similar between treatment groups at baseline (**Table 4**).

Table 4. Baseline Characteristics of All Randomized Patients[4]

	Avalide (n=328)	Irbesartan Monotherapy (n=106)	HCTZ Monotherapy (n=104)
Age (mean), years	55.1	55.3	56.0
Male (%)	55.2	46.2	59.6
Ethnicity			
White (%)	82.6	89.6	82.7
Black (%)	15.2	8.5	14.4
Asian	1.8	0	1.9
Native Hawaiian/ other Pacific Islander[a]	0.3	1.8	1.0
Weight (kg)	87.6	88.2	88.4
Baseline BP (mm Hg)	161.7/97.5	161.4/97.9	162.0/97.6
Diabetes (%)	14.3	13.2	12.5
Hyperlipidemia (%)	44.5	42.5	35.6
Prior antihypertensive therapy (%)	52.4	49.1	45.2
[a]Native Hawaiian/other Pacific Islander/American-Indian/Alaska native			

Reduction in SeSBP at Week 8 (primary endpoint) was significantly greater in the Avalide group (-27.1 mm Hg) compared to either irbesartan (-22.1 mm Hg; *P*=0.0016) or HCTZ (-15.7 mm Hg; *P*<0.0001) monotherapy. Avalide also significantly reduced SeDBP at Week 8 (-14.6 mm Hg) compared to either irbesartan (-11.6 mm Hg; *P*=0.0013) or HCTZ (-7.3 mm Hg; *P*<0.0001). The percentage of patients who achieved an overall BP control of <140/90 mm Hg at Week 8 was 53.4%, 40.6%, and 20.2% for Avalide, irbesartan, and HCTZ, respectively (*P*=0.0254 vs irbesartan; *P*<0.0001 vs HCTZ). Efficacy results are reported in **Table 5**.

Table 5. Comparison of Efficacy Results of Combination versus Monotherapy[4]

	Avalide	Irbesartan Monotherapy[b]	HCTZ Monotherapy[b]
Primary endpoint			
Δ in SeSBP from baseline, Week 8 (mm Hg)	–27.1	–22.1 (*P*=0.0016)	–15.7 (*P*<0.0001)
Secondary endpoints			
Δ in SeDBP from baseline, Week 8 (mm Hg)	–14.6	–11.6 (*P*=0.0013)	–7.3 (*P*<0.0001)
BP Control[a], Week 2 (%)	26.5	20.8 (*P*=NS)	14.4 (*P*<0.05)
BP Control[a], Week 4 (%)	44.5	29.2 (*P*<0.01)	17.3 (*P*<0.0001)
BP Control[a], Week 8 (%)	53.4	40.6 (*P*<0.05)	20.2 (*P*<0.0001)
BP Control[a], Week 12 (%)	55.8	34.0 (*P*<0.0001)	25.0 (*P*<0.0001)

Δ, mean change; NS, not significant
[a] defined as <140/90 mm Hg
[b] *P*-value for comparison to Avalide

Treatment was well tolerated in all three study groups. The overall frequency of AEs was similar in all three treatment arms: 47.0% with Avalide, 45.3% with irbesartan, and 39.4% with HCTZ. Treatment-related AEs were more common in the Avalide group (14.3%) versus 11.3% and 7.7% in the irbesartan and HCTZ groups, respectively. The rates of pre-specified AEs were 10.7%, 6.6%, and 6.7% for Avalide, irbesartan, and HCTZ, respectively. Six serious AEs were reported in the Avalide group, only one of which was considered related to study drug (mild hypokalemia), and three serious AEs were reported in the HCTZ group. There were no deaths during the study. Safety results are provided in**Table 6**.

Table 6. Safety Results at Week 12 (All Randomized Patients)[4]

	Avalide (n=328)	**Irbesartan Monotherapy (n=106)**	**HCTZ Monotherapy (n=104)**
Adverse Events, n (%)	154 (47.0)	48 (45.3)	41 (39.4)
Pre-specified AEs, n (%)	35 (10.7)	7 (6.6)	7 (6.7)
Dizziness	10 (3.0)	4 (3.8)	1 (1.0)
Headache	18 (5.5)	4 (3.8))	5 (4.8)
Hyperkalemia	4 (1.2)	0	1 (1.0)
Hypokalemia	3 (0.9)	0	0
Hypotension	3 (0.9)	0	0
Syncope	0	0	1 (1.0)
Serum potassium < 3.0 mmol/L	0	0	0
Serum potassium > 6.0 mmol/L	4 (1.2)	0	0
Serious AEs, n (%)	6 (1.8)	0	3 (2.9)
Treatment-related AEs, n (%)	47 (14.3)	12 (11.3)	8 (7.7)
Discontinuations due to AEs, n (%)	22 (6.7)	4 (3.8)	5 (4.8)

The authors concluded that Avalide combination therapy was effective, had a favorable safety profile and was well tolerated in patients with moderate hypertension when used as initial treatment or in those uncontrolled on monotherapy. The authors also found that Avalide achieved rapid and sustained reductions in SBP and DBP.

Please note that neither Bristol-Myers Squibb nor sanofi-aventis recommends the use of Avalide in any manner inconsistent with that described in the Full Prescribing Information. Please consult the Full Prescribing Information for Avalide, including the **boxed WARNING regarding Use in Pregnancy.**

I hope you find this information helpful. If you have further questions or require additional information, please contact the Bristol-Myers Squibb Medical Information Department at 1–800–321–1335.

Sincerely,

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Enclosure(s): Avalide Full Prescribing Information

References:

1. Neutel JM, Franklin SS, Oparil S, Bhaumik A, Ptasznska A, Lapuerta P. Efficacy and safety of irbesartan/HCTZ combination therapy as initial treatment for rapid control of severe hypertension. *J Clin Hypertens.* 2006;8:850-857.

2. Neutel JM, Franklin SS, Bhaumik A, et al. Irbesartan/HCTZ combination therapy as initial treatment for severe hypertension to achieve rapid BP control [poster]. Presented at 21st Annual Scientific Meeting of the American Society of Hypertension; 2006 May 16-20; New York City, NY, USA. Poster P-106.

3. Neutel JM, Franklin SS, Bhaumik A, et al. Irbesartan/HCTZ combination therapy as initial treatment for severe hypertension to achieve rapid BP control [abstract]. Presented at 21st Annual Scientific Meeting of the American Society of Hypertension; 2006 May 16-20, P-106; New York City, NY, USA.

4. Neutel JM, Franklin SS, Lapuerta P, et al. A comparison of the efficacy and safety of irbesartan/HCTZ combination therapy with irbesartan and HCTZ monotherapy in the treatment of moderate hypertension. *J Hum Hypertens*. 2007;Epub.