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Irbesartan/Hydrochlorothiazide
In Moderate to Severe Hypertension

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Contents

Abstract

▲ The fixed-dose combination of irbesartan/hydrochlorothiazide (HCTZ) is approved in the US for use as initial therapy in patients who are likely to need multiple agents to achieve their blood pressure (BP) goals.

▲ In a 12-week, randomized, double-blind, multicentre trial in 538 patients with moderate hypertension that was untreated or uncontrolled by monotherapy, the mean reduction from baseline in seated systolic BP (SeSBP) at week 8 (primary endpoint) was significantly greater with irbesartan/HCTZ than with either irbesartan or HCTZ as monotherapy.

▲ In addition, the proportion of patients with moderate hypertension achieving controlled BP (SeSBP <140 mmHg/seated diastolic BP [SeDBP] <90 mmHg) at 12 weeks was significantly greater with irbesartan/HCTZ combination therapy than with irbesartan or HCTZ monotherapy.

▲ In a 7-week, randomized, double-blind, multicentre trial in 697 patients with severe hypertension that was untreated or uncontrolled by monotherapy, a significantly greater proportion achieved a trough SeDBP of <90 mmHg following 5 weeks of combination therapy with irbesartan/HCTZ compared with irbesartan monotherapy (primary endpoint).

▲ Furthermore, the proportion of patients with severe hypertension achieving controlled BP of <140/90 mmHg was significantly greater at all timepoints of the trial compared with irbesartan monotherapy.

▲ Irbesartan/HCTZ combination therapy had a similar tolerability profile to irbesartan and HCTZ monotherapy. Most adverse events were of mild to moderate intensity.

Features and properties of irbesartan/hydrochlorothiazide (IRB/HCTZ) [Avalide®]	
Featured indication	
Initial therapy in patients with hypertension who were likely to need multiple drugs to achieve their BP goals.	
Mechanism of action	
Antihypertensive	Combined angiotensin II receptor antagonist (IRB) and thiazide diuretic (HCTZ)
Dosage and administration	
Initial therapy	Initiate with IRB/HCTZ 150 mg/12.5 mg once daily for 1–2 wk and titrate as needed up to a maximum of 300 mg/25 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profiles (IRB 150 mg, HCTZ 12.5 mg single oral doses in healthy volunteers)	
Mean area under the plasma concentration-time curve (AUC) [IRB] and AUC from time 0 to 9 h (HCTZ)	9.7 μg • h/mL (IRB) 351 ng • h/mL (HCTZ)
Mean maximum plasma concentration (C_{max})	1.9 μg/mL (IRB) 70 ng/mL (HCTZ)
Mean time to C_{max}	1.5 h (IRB) 1.5–4 h (HCTZ)
Mean elimination half-life	11–15 h (IRB) ≈8 h (HCTZ)
Mean renal clearance	0.18 L/h (IRB) 20.7 L/h (HCTZ)
Adverse events	
Most frequent	Headaches, dizziness

According to WHO assessments, cardiovascular disease is the leading cause of death worldwide and is predicted to remain a significant problem.[1] Current estimates indicate that the global adult hypertensive population could exceed 1.5 billion by 2025.[2] Elevated blood pressure (BP), as determined by both systolic and diastolic measurements, is recognized as having a direct relationship with cardiovascular morbidity and mortality.[3] Patients with elevated BP have an increased risk of heart failure, myocardial infarction, peripheral artery disease, renal failure, retinopathy, stroke and dementia.[3]

Both the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7)[4] and the European Society for Hypertension guidelines[3] recognize the urgency of treating essential hypertension. Both recommend initial combination therapy, from two or more classes of antihypertensive agents, to lower BP within weeks rather than months in patients with stage 2 hypertension,[4] or in patients with BP in the grade 2 or 3 range or those at a high or very high cardiovascular risk.[3] In patients with essential hypertension, JNC-7 guidelines indicate that the primary goal of therapy is to promptly reduce seated systolic BP (SeSBP) to <140 mmHg and seated diastolic BP (SeDBP) to <90 mmHg.[4]

Combination therapy increases the likelihood that BP goals will be achieved in a more timely fashion.[4] In addition, combination therapy may achieve greater BP reductions with lower dosages of the component drugs, thus reducing the likelihood of adverse events. Furthermore, fixed-dose combination agents may simplify treatment and be more convenient for the majority of patients to use.[4] However, an individualized strategy of initiating therapy with a thiazide diuretic and subsequently optimizing with other agents in combination may be more appropriate for some patients.[5]

A fixed-dose combination of the angiotensin II type 1 (AT_1) receptor antagonist irbesartan and the thiazide diuretic hydrochlorothiazide (HCTZ) [irbesartan/HCTZ; Avalide®][1] has been approved in the US for the initial treatment of hypertension in patients who are likely to need multiple drugs to achieve their BP goals, and is the focus of this review.[6]

1. Pharmacodynamic Profile

The pharmacodynamic properties of irbesartan[7] and HCTZ[8] are well documented and their mechanism of action and pharmacodynamic effects are only briefly discussed in this section.

- Irbesartan is an AT_1 receptor antagonist that exerts an inhibitory effect on the pressor response to angiotensin II. Antagonism of AT_1 receptors elicits vasodilation and a reduced production of vasopressin and aldosterone, the combined effect of which reduces BP in hypertensive patients.[7]
- Single oral doses of irbesartan 150 or 300 mg resulted in complete (100%) inhibition of the pressor effect of angiotensin II infusions 4 hours after treatment with the drug in healthy volunteers.[6] The level of inhibition at 24 hours after administration was 40% with irbesartan 150 mg and 60% with 300 mg.
- Long-term administration of irbesartan brought about a 1.5- to 2-fold increase in plasma angiotensin II levels and a 2- to 3-fold increase in plasma renin levels in patients with hypertension. Long-term irbesartan (up to 300 mg/day) did not affect the glomerular filtration rate, renal plasma flow or filtration fraction.[6] In patients with hypertension, long-term administration of irbesartan had no clinically meaningful effect on fasting triglycerides, total cholesterol, high-density lipoprotein-cholesterol or fasting glucose concentrations.[6]
- HCTZ reduces sodium reabsorption in the distal convoluted tubule of the kidney, thus reducing osmotic pressure, causing less water to be reabsorbed and thereby lowering plasma volume and reducing blood pressure.[6] Diuresis begins within 2 hours of oral administration of HCTZ, peaks at 4 hours and lasts for ≈6–12 hours.[6]

1 The use of trade names is for identification purposes only and does not imply endorsement.

2. Pharmacokinetic Profile

Pharmacokinetic data on the irbesartan/HCTZ fixed-dose combination are not available. However, the pharmacokinetics of irbesartan are unaffected by the addition of HCTZ,[9] and therefore the profiles of the two drugs from studies in healthy volunteers are reported separately[10-14] and supplemented by data from the manufacturer's prescribing information where appropriate.[6] This section focuses on pharmacokinetic data for irbesartan 150 and 300 mg and HCTZ 12.5 and 25 mg, the recommended dosages of these agents when used in combination for the treatment of essential hypertension.[6]

Irbesartan

- Irbesartan is an orally active compound, which unlike olmesartan,[15] does not require biotransformation for activation.[16] It has a mean oral bioavailability of ≈60–80%.[11]
- Mean maximum plasma concentrations (C_{max}) increased in a linear, less than dose-proportional manner and the mean area under the plasma concentration-time curve (AUC) increased in a linear, dose-proportional manner following single or multiple doses of irbesartan 150–600 mg once daily in healthy volunteers.[10]
- Absorption was rapid, with C_{max} values of 1.9 and 2.9 μg/mL reached within a median time of 1.5 hours following single oral doses of irbesartan 150 or 300 mg;[10] mean AUC values were 9.7 and 20.0 μg • h/mL, respectively.[10]
- Multiple doses resulted in little accumulation and steady-state concentrations were achieved within 3 days with once-daily administration.[10] Mean C_{max} values of 2.04 and 3.3 μg/mL, and mean AUC values of 9.3 and 19.8 μg • h/mL were achieved with multiple-dose irbesartan 150 and 300 mg/day.[10]
- Irbesartan is ≥90% bound to serum proteins, primarily albumin and α_1-acid glycoprotein,[6] and has a mean steady-state volume of distribution of 53–93 L in healthy volunteers.[11]
- Metabolism of irbesartan is predominantly through glucuronidation and oxidation.[16] It is primarily oxidized *in vitro* by the cytochrome P450 (CYP) isoenzyme 2C9 with negligible metabolism via CYP3A4.[17]
- In healthy volunteers, mean renal clearance showed little variation between single oral doses of irbesartan 50 and 150 mg, with a mean value of 0.18 L/h at the 150 mg dose.[11] The mean elimination half-life was 11–15 hours in healthy volunteers receiving irbesartan 150 and 300 mg once daily.[6,10]
- One and 6 hours after oral administration of ^{14}C-labelled irbesartan 150 mg, 81% and 76% of circulating plasma radioactivity was accounted for by the unchanged compound.[16] Eight metabolites were identified, each with minimal pharmacological activity.[16] The primary circulating metabolite was an inactive conjugated irbesartan glucuronide that accounted for approximately 6% of plasma radioactivity at the 1-hour timepoint.[16]
- Approximately 17% of the radiolabelled dose was recovered in the urine and 54% in the faeces.[16]

Hydrochlorothiazide

- Mean C_{max} and AUC values increased in a dose-dependent manner following single oral doses of HCTZ (12.5–100 mg) in two studies in healthy volunteers.[12,13] In one study, single-dose HCTZ 12.5 mg resulted in a mean C_{max} of 70 ng/mL after 1.5–4 hours and a mean AUC from time zero to 9 hours (AUC_9) of 351 ng • h/mL.[13] Following single oral doses of HCTZ 25 mg, mean C_{max} values of 127[12] and 142[13] ng/mL were attained after 2.4[12] and 2–5[13] hours, respectively, with a mean AUC from time zero to 36 hours of 978 ng • h/mL[12] and a mean AUC_9 of 613 ng • h/mL.[13] Based on urinary recovery, the bioavailability of HCTZ 12.5 and 25 mg was 63–72%.[13,14]
- Mean renal clearance showed little variation and averaged 20.7[13] L/h for the 12.5 dose and 19.9[13] or 15.4[12] L/h for the 25 mg dose.
- HCTZ is eliminated predominantly unchanged by the kidney,[12,13] with a mean terminal elimination half-life of 8.2 hours for HCTZ 25 mg.[12] At least 61% of an oral dose of HCTZ is eliminated unchanged within 24 hours.[6]

Special Populations

● The pharmacokinetics of irbesartan were not altered to a clinically significant extent in women versus men, in the elderly, in patients with mild to severe renal impairment or in patients with mild or moderate hepatic impairment. No dosage adjustment is needed in these patient groups, although irbesartan/HCTZ should not be commenced in patients with renal impairment and volume depletion until the volume depletion has been corrected.[6]

Potential Drug Interactions

● Irbesartan is predominantly metabolized via CYP2C9[17] and therefore has the potential to interact with other drugs that are metabolized by or inhibit this isoenzyme. The formation of oxidized metabolites of irbesartan was inhibited by the CYP2C9 substrates/inhibitors sulfenazole, tolbutamide and nifedipine *in vitro*.[6]

In clinical studies, concomitant administration of irbesartan had a negligible effect on the pharmacokinetics of digoxin. Similarly, concomitant nifedipine or HCTZ had a negligible effect on the pharmacokinetics of irbesartan.[6]

3. Therapeutic Efficacy

The therapeutic efficacy of irbesartan/HCTZ combination therapy in the treatment of moderate[18] or severe[19] essential hypertension in adult patients (aged ≥18 years) has been evaluated in two randomized, double-blind, active-controlled, multicentre, fully published trials (n = 538[18] and 697[19]). Patients in these trials had moderate[18] or severe[19] hypertension that was previously untreated or uncontrolled by monotherapy; in both trials, prior monotherapy was defined as treatment with a single antihypertensive medication for at least 4 weeks.[18,19]

Moderate Hypertension

Untreated patients with moderate hypertension were enrolled if they had an SeSBP of 160–179 mmHg or an SeDBP of 100–109 mmHg.[18] Patients previously receiving monotherapy were enrolled if they had SeSBP of 150–179 mmHg or SeDBP of 95–109 mmHg.[18] Patients with severe hypertension (SeSBP ≥180 mmHg or SeDBP ≥110 mmHg), those with SeSBP <130 mmHg, malignant, accelerated or secondary hypertension were excluded from the trial. Following a single-blind, placebo washout period of 21 days' duration, eligible patients were randomized 3 : 1 : 1 to receive either fixed-dose irbesartan/HCTZ 150 mg/12.5 mg once daily for 2 weeks followed by a forced titration to irbesartan/HCTZ 300 mg/25 mg once daily for 10 weeks (n = 328), irbesartan 150 mg once daily for 2 weeks followed by irbesartan 300 mg once daily for 10 weeks (n = 106), or HCTZ 12.5 mg once daily for 2 weeks followed by HCTZ 25 mg once daily for 10 weeks (n = 104).[18]

Baseline characteristics were similar for each treatment arm, with a mean age of approximately 55 years and a mean seated BP of 161.7/97.5 mmHg.[18] The primary efficacy variable was defined as the mean reduction from baseline in SeSBP at week 8.[18] Secondary endpoints included SeSBP at week 12, SeDBP at weeks 8 and 12 and the proportion of patients with controlled BP at weeks 8 and 12.[18] Controlled BP was defined as SeSBP <140 mmHg and SeDBP <90 mmHg as defined by JNC-7 guidelines.[4] All BP measurements were made at trough and efficacy analyses were conducted in the modified intent-to-treat population.[18]

● Irbesartan/HCTZ combination therapy was more efficacious than monotherapy with either irbesartan or HCTZ in reducing BP in patients with moderate hypertension.[18] Both the rate and the extent of BP decline were greater following combination therapy with irbesartan/HCTZ than with monotherapy.[18]

● The mean reduction in SeSBP from baseline following 8 weeks of combination therapy with irbesartan/HCTZ was 27.1 mmHg, which was significantly greater than that with irbesartan (22.1 mmHg, $p = 0.0016$) or HCTZ (15.7 mmHg, $p < 0.0001$) monotherapy (primary endpoint).[18]

● In patients stratified according to whether they were previously untreated or uncontrolled by mono-

therapy, the mean reduction in SeDBP was 28.2 mmHg following 8 weeks' irbesartan/HCTZ in patients uncontrolled by monotherapy and 26.0 mmHg in previously untreated patients.[18]

- In support of a more rapid decline in BP following combination therapy, significantly greater reductions in SeDBP (9.3 vs 7.3 and 5.5 mmHg) and SeSBP (17.9 vs 13.9 and 10.2 mmHg) were seen with irbesartan/HCTZ than with irbesartan or HCTZ monotherapy as early as week 2 (p-values not reported).[18]
- A significantly greater reduction from baseline in SeDBP was seen at week 8 in irbesartan/HCTZ recipients than in irbesartan monotherapy or HCTZ monotherapy recipients (14.6 vs 11.6 and 7.3 mmHg; $p = 0.0013$ and $p < 0.0001$).[18] At week 12, reductions in SeDBP (15.2 vs 11.1 and 7.8 mmHg) and SeSBP (28.3 vs 19.5 and 16.5 mmHg) were significantly greater with irbesartan/HCTZ than with irbesartan monotherapy or HCTZ monotherapy (p-values not reported).[18]
- The proportion of patients achieving controlled BP was significantly greater with irbesartan/HCTZ than with irbesartan monotherapy or HCTZ monotherapy at both week 8 (53.4% vs 40.6% and 20.2%; $p < 0.05$ and $p < 0.0001$) and week 12 (55.8% vs 34.0% and 25.0%; both $p < 0.0001$).[18]

Severe Hypertension

Patients were enrolled if they were previously untreated and had SeDBP ≥110 mmHg or if they had SeDBP ≥100 mmHg despite receiving prior antihypertensive monotherapy.[19] Patients with an SeSBP of ≥220 mmHg or an SeDBP of ≥120 mmHg were excluded, as were patients with suspected secondary hypertension. Patients who subsequently had an SeDBP of ≥100 mmHg on two consecutive visits during a 7-day, single-blind, randomized, placebo run-in period (during which no antihypertensive agents were administered) were considered eligible. These patients were randomized 2 : 1 to receive either fixed-dose irbesartan/HCTZ 150 mg/12.5 mg once daily for 1 week and then force-titrated to fixed-dose irbesartan/HCTZ 300 mg/25 mg once daily for the remaining 6 weeks (n = 468) or irbesartan 150 mg once daily for 1 week followed by forced titration to irbesartan 300 mg once daily for 6 weeks (n = 269).[19]

Baseline characteristics were similar in each treatment arm with a mean age of 52.2 years in the irbesartan/HCTZ group and 52.9 years in the irbesartan group.[19] Mean seated BP was 171.5/113.4 mmHg in the irbesartan/HCTZ group and 171.6/113.3 mmHg in the irbesartan group. The primary outcome measure was the proportion of patients with SeDBP <90 mmHg at week 5.[19] Secondary efficacy endpoints included the proportion of patients achieving a controlled seated BP of <140/90 mmHg, the proportion of patients achieving a change from baseline in SeSBP and SeDBP at all visits, and the proportion with SeDBP <90 mmHg at weeks 1, 3 and 7 of treatment.[19]

- In patients with severe hypertension, a significantly greater proportion of irbesartan/HCTZ recipients than irbesartan monotherapy recipients achieved an SeDBP of <90 mmHg at week 5 (47.2% vs 33.2%; $p = 0.0005$) [primary endpoint].[19]
- In addition, a significantly greater proportion of irbesartan/HCTZ recipients than irbesartan monotherapy recipients achieved an SeDBP of <90 mmHg at week 1 (15.2% vs 9.2%; $p = 0.0317$), week 3 (≈40% vs ≈25%; $p = 0.0002$) [data estimated from graph] and week 7 (51.9% vs 32.8%; $p < 0.0001$).[19]
- The percentage of patients achieving SeDBP <90 mmHg ($p < 0.001$ at weeks 3, 5 and 7) was 14–19% higher with combination therapy than with irbesartan monotherapy during weeks 3–7 of the trial.[19]
- A significantly greater proportion of irbesartan/HCTZ than irbesartan monotherapy recipients achieved seated BP <140/90 mmHg at week 1 (9.2% vs 4.4%; $p = 0.023$), week 3 (30.6% vs 12.7%; $p < 0.001$), week 5 (34.6% vs 19.2%; $p < 0.001$) and week 7 (37.8% vs 21.4%; $p < 0.001$).[19]
- The reduction from baseline in both SeDBP and SeSBP was significantly greater in recipients of irbesartan/HCTZ combination therapy than in patients receiving irbesartan monotherapy at all timepoints in the trial ($p = 0.0006$ for SeSBP at all

timepoints and for SeDBP at week 1, $p < 0.0001$ for SeDBP at weeks 3, 5 and 7). At week 3, combination therapy reduced mean SeDBP by >20 mmHg and SeSBP by 27 mmHg, whereas monotherapy required 7 weeks to achieve similar decreases.[19]

- Exposure to severe levels of DBP (defined as SeDBP of ≥110 mmHg) was significantly ($p = 0.004$) less (difference of 26 patient-weeks for every 100 patients treated) in patients who received irbesartan/HCTZ than in those who received irbesartan monotherapy.[19]

4. Tolerability

- Irbesartan/HCTZ was generally well tolerated in patients with moderate or severe hypertension, according to the results of the two trials reviewed in section 3.[18,19]
- The overall incidence of treatment-related adverse events in patients with moderate hypertension was 14.3% with irbesartan/HCTZ, 11.3% with irbesartan and 7.7% with HCTZ.[18] The incidence of adverse events related to BP-lowering therapy was prespecified as secondary outcome measure[18] and is shown in figure 1; headaches and dizziness were the most frequent events.[18] Of 328 patients in the irbesartan/HCTZ treatment arm, one serious

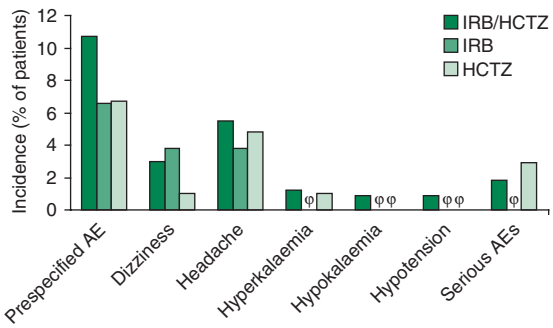

Fig. 1. Tolerability of irbesartan/hydrochlorothiazide (IRB/HCTZ) in patients with moderate essential hypertension. Results of a randomized, double-blind, multicentre trial. Data presented are the incidence of prespecified adverse events (AEs) most commonly observed with IRB/HCTZ combination therapy and IRB and HCTZ monotherapy. Patients received IRB/HCTZ (target dosage 300 mg/25 mg once daily) [n = 328], IRB monotherapy (target dosage 300 mg once daily) [n = 100] or HCTZ monotherapy (target dosage 25 mg once daily) [n = 104] for 12 weeks.[18] φ = incidence of 0%.

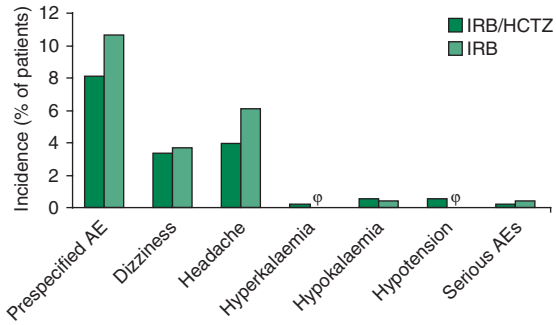

Fig. 2. Tolerability of irbesartan/hydrochlorothiazide (IRB/HCTZ) in patients with severe essential hypertension. Data presented are the incidence of prespecified adverse events (AEs) most commonly observed with IRB and HCTZ monotherapy. Results of a randomized, double-blind, multicentre trial. Patients received IRB/HCTZ (target dosage 300 mg/25 mg once daily) [n = 468] or IRB (target dosage 300 mg once daily) [n = 229] for 7 weeks.[19] φ = incidence of 0%.

treatment-related adverse event of hypokalaemia was reported, which was mild in severity.[18]

- The incidences of discontinuation due to an adverse event after 12 weeks of therapy were 6.7%, 3.8% and 4.8% in the irbesartan/HCTZ, irbesartan and HCTZ groups, respectively.[18] Four patients withdrew because of dizziness and three because of hypotension in the irbesartan/HCTZ group; these events mainly occurred in patients with controlled BP following forced titration.[18] No instance of abnormal change in total cholesterol was observed in any patient.[18]
- In patients with severe hypertension, the overall incidence of prespecified adverse events considered related to antihypertensive therapy was 8.8% with irbesartan/HCTZ and 11.5% with irbesartan monotherapy.[19] These were mostly restricted to headache and dizziness and were of mild to moderate intensity (figure 2). No serious adverse events that were thought to be treatment-related were reported in either treatment arm.[19] The frequency of discontinuation due to adverse events after 7 weeks of therapy was 1.9% in irbesartan/HCTZ recipients and 2.2% in the irbesartan monotherapy recipients.[19] Three patients withdrew in the combination therapy group because of treatment-related dizziness, fatigue and hypotension.[19]

5. Dosage and Administration

In patients with hypertension who are likely to need multiple drugs to achieve BP goals, initial therapy with irbesartan/HCTZ may be started at a dosage of 150 mg/12.5 mg once daily.[6] After 1–2 weeks, the dosage can be increased to a maximum of 300 mg/25 mg once daily, as needed to control BP. Irbesartan/HCTZ may be administered with or without food and with other antihypertensive agents[6] Irbesartan/HCTZ carries a black-box warning stating that it should be discontinued as soon as possible when pregnancy is detected; use of drugs that act directly on the renin-angiotensin system during the second and third trimesters can cause injury and even death in a developing foetus.[6] Local prescribing information should be consulted for other contraindications, warnings or recommended dosage adjustments in special patient groups.

6. Irbesartan/Hydrochlorothiazide in Moderate to Severe Hypertension: Current Status

Irbesartan/HCTZ is approved in the US for use as initial therapy in patients with hypertension who are likely to need multiple agents to achieve their BP goals.[6] Previously, the combination was approved for use only in patients with hypertension whose BP was not adequately controlled with monotherapy. Large, well controlled, short-term trials have shown a greater and more rapid reduction in BP with irbesartan/HCTZ combination therapy versus irbesartan or HCTZ monotherapy in patients with moderate or severe hypertension that was previously untreated or uncontrolled by monotherapy.[18,19] Irbesartan/HCTZ combination therapy was generally well tolerated and showed a similar tolerability profile to each agent as monotherapy.[18,19]

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