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Telmisartan/Hydrochlorothiazide

In the Treatment of Essential Hypertension

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Contents

Abstract

▲ Oral telmisartan/hydrochlorothiazide (HCTZ) combines two antihypertensive agents, a selective angiotensin II receptor antagonist with a long half-life and once-daily administration, and a thiazide diuretic.

▲ In two large, 8-week, double-blind trials, patients with hypertension unresponsive to monotherapy who received combined telmisartan/HCTZ 80/12.5 or 40/12.5 mg/day, achieved significantly larger reductions in diastolic and systolic blood pressure (BP), than recipients of continued telmisartan monotherapy ($p < 0.05$ for all). Compliance with telmisartan/HCTZ 80/12.5 mg/day was 98.9%.

▲ In patients with hypertension, telmisartan/HCTZ resulted in similar BP reductions to oral enalapril/HCTZ and atenolol/HCTZ in 26-week double-blind trials and greater reductions than oral losartan/HCTZ 50/12.5 mg/day in a 6-week randomised open-label trial ($p < 0.001$).

▲ Up to one-third of patients with hypertension initially responsive to telmisartan 40 or 80 mg/day in a 4-year study required the eventual addition of HCTZ 12.5 or 25 mg/day and/or another agent to maintain BP control. BP was controlled in about 75% of these by adding only HCTZ.

▲ In clinical trials of up to 4 years, including elderly patients, telmisartan/HCTZ had similar tolerability to placebo, with few reports of hypokalaemia. Most adverse events were mild to moderate.

Features and properties of telmisartan/hydrochlorothiazide (MicardisPlus®, Micardis®HCT, PritorPlus®)	
Indications	
Second-line therapy of essential hypertension not adequately controlled by telmisartan (TEL) monotherapy (EU and US) or hydrochlorothiazide (HCTZ) monotherapy (US).	
Mechanism of action	
Antihypertensive	Combined angiotensin II receptor antagonist (TEL) and thiazide diuretic (HCTZ)
Dosage and administration	
Approved dose	US: TEL/HCTZ 80/12.5 mg/day up to 160/25 mg/day; EU: TEL/HCTZ 40/12.5 or 80/12.5 mg/day
Route and frequency of administration	Oral, once daily
Pharmacokinetic profile (oral TEL 80 mg/day for 28 days or oral HCTZ 12.5mg single dose)	
Peak plasma concentration	TEL: 465 ng/mL; HCTZ: 70 ng/mL
Time to peak plasma concentration	TEL: 1h; HCTZ: 1.5–4h
Area under the plasma concentration-time curve (AUC)	TEL: 2651 ng • h/mL (AUC_{∞}); HCTZ: 351 ng • h/mL (AUC_{9h})
Elimination half-life	TEL:≈24h; HCTZ: 5.6–14.8h
Most common adverse events	
Upper respiratory tract infections, dizziness, sinusitis, fatigue and diarrhoea	

Telmisartan, an angiotensin II subtype 1 (AT_1) receptor antagonist, and hydrochlorothiazide (HCTZ), a thiazide diuretic, are each effective in the treatment of mild to moderate hypertension.[1] However, many patients with essential hypertension are, either from the time of diagnosis or later, inadequately controlled by monotherapy.[2-5] Fixed-dose formulations such as telmisartan/HCTZ (Micardis-Plus®[1], Micardis®HCT, PritorPlus®) have been developed to encourage compliance and better control of hypertension in patients who need more than one antihypertensive agent to control their blood pressure (BP).

The use of telmisartan in hypertension was reviewed shortly after its introduction.[6] This review provides information on the efficacy of telmisartan/HCTZ combinations in the treatment of essential hypertension compared with telmisartan or HCTZ alone or with other drugs. Unless stated otherwise, telmisartan and HCTZ were administered orally.

1. Pharmacodynamic Profile

Telmisartan

- In an *in vitro* study in rat aortic smooth muscle membrane, where angiotensin receptors are exclusively of the AT_1 subtype, [^{3}H]telmisartan inhibited the binding of [^{125}I]angiotensin II to AT_1 receptors (dissociation constant [K_D] ≈1.7 nmol/L).[7] Telmisartan had a higher affinity than angiotensin II for these receptors. Dissociation was slow, with a dissociation half-life ($t_{½diss}$) of about 75 minutes compared with 14.5 minutes for angiotensin II, and there was no reassociation of the drug.[7] Telmisartan concentration-dependently antagonised the vasoconstrictive effect of angiotensin II in rat mesenteric artery at doses of 1.0–10 nmol/L ($p < 0.05$) and was more effective than irbesartan and losartan at this concentration ($p < 0.01$ for both).[8]
- A single 0.1 mg/kg intravenous dose of telmisartan in male normotensive Wistar rats inhibited the pressor response to exogenous angiotensin II.[7] Intravenous telmisartan 1 mg/kg blocked the angiotensin II receptors by a mean 95% at peak and 78% after 24 hours; at this dose, candesartan and telmisartan exhibited a comparable effect on the BP response to angiotensin II but telmisartan provided 10-fold greater activity than irbesartan.[7]
- In a randomised, double-blind, placebo-controlled, parallel-group study in 48 healthy male volunteers, telmisartan showed dose-dependent inhibition of intravenous angiotensin II-induced increases in diastolic BP (DBP), including virtually complete inhibition at a 40 or 80mg dose.[9] Onset of inhibition occurred within 0.3–1.1 hours of administration of a single dose of telmisartan (20–80mg). Inhibition of >25% of the angiotensin II response was evident after 27–41 hours, with large individual variation, and a response significantly different from that with placebo was evident after 48 hours ($p < 0.05$).
- A single-blind, parallel-group study in 20 healthy male volunteers found the angiotensin II receptor blockade after 1 week of telmisartan 80mg once daily significantly lower at 24 hours than at 4 hours after administration (32–36% vs 60–63%, p value not stated).[10] Blockade was measured by either inhibition of the pressor response to angiotensin I or displacement of labelled angiotensin II; inhibition of pressor response at both 4 and 24 hours post-dose (trough) was significant ($p < 0.001$ vs baseline).
- Trough inhibition results for losartan 100mg once daily, were similar to those of telmisartan 80mg, but the addition of lisinopril 20mg once daily to either agent significantly increased the trough inhibitory effect to 79% with telmisartan and 76% with losartan ($p < 0.001$ for both comparisons vs respective monotherapy).[10] There was a significant correlation ($r = -0.25$, $p = 0.05$) between the 24-hour trough inhibitory effect on the pressor response to angiotensin I and the change in systolic BP (SBP).
- The effect of telmisartan on renal function was assessed in 25 drug-free patients with hypertension, randomised to telmisartan 40 or 80 mg/day or placebo for 15 days, after 1 week on a Na^+ 100 mmol/day diet (continued throughout the study).[11,12] On day

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

1, urinary Na^+ excretion was significantly higher in the telmisartan 80 mg/day than the placebo group, for both the first 8 hours (7.5 vs 3.6 mmol/h for the first 4 hours, $p = 0.01$ and 7.9 vs 2.8 mmol/h for the second 4 hours, $p < 0.01$) and over the entire first 24 hours post-dose (60.7 vs 6.1 mmol, $p = 0.01$).[11] A significant difference continued for 2 more days ($p = 0.05$) and was also evident for hours 4–8 post-dose on day 8 (p value not stated in abstract).[12] There was no effect on K^+ or uric acid.[11]

- In another healthy volunteer study, in the first 3 hours after telmisartan administration there were significant increases, versus placebo, in urine flow (0.086, 0.083, 0.131 L/h with telmisartan 20, 40 or 80mg vs 0.059 L/h with placebo, p value not stated) and Na^+ and K^+ excretion (results not reported).[9]
- Studies looking at the effects of telmisartan in hypertension that will provide information on end-organ damage (renal, cardiac and vascular) are ongoing.[13]

Hydrochlorothiazide (HCTZ)

- In eight healthy volunteers who received HCTZ 12.5–75mg in random order at least 2 weeks apart, 12.5 or 25mg provided a diuretic effect after the second hour. The average urine output of 2009 and 2005mL (HCTZ 12.5 and 25mg) in the first 10 hours was significantly different from diuresis with placebo (1208mL; $p < 0.001$ for both comparisons).[14] A natriuretic effect persisted for the 10-hour observation period, with Na^+ excretion of 136.7 mmol after HCTZ 12.5mg compared with 36.9 mmol with placebo ($p < 0.001$). Higher HCTZ doses had a similar effect. K^+ excretion in the first 10 hours was significantly different from that with placebo only for HCTZ 25–75mg (46.7–55.7 mmol vs placebo 29.5 mmol; $p < 0.05$).[14]
- Natriuresis and kaliuresis both increased significantly ($p \leq 0.05$ for all comparisons) in nine Black and nine White patients with hypertension (baseline supine BP 150/88 and 144/86mm Hg, respectively), who received HCTZ 25mg after 7 days on a Na^+ and K^+-controlled diet.[15] Following the diet, 24-hour Na^+ excretion increased slightly in Black patients from a pre-diet baseline of 117 to 122 mmol, compared with a decrease from 140 to 117 mmol in Whites. A further increase to 265 mmol in Black patients and an increase to 255 mmol in Whites occurred after treatment with HCTZ. With HCTZ, 24-hour K^+ excretion increased from 43 mmol at baseline to 66 mmol in Blacks. Although significant compared with baseline ($p \leq 0.05$), the increase in K^+ excretion in Black patients was significantly less ($p \leq 0.05$) than the increase from 53 mmol at baseline to 86 mmol in Whites. Post-dose, urinary aldosterone excretion followed a circadian pattern in White but not Black patients, increasing in Black patients only after 24 hours. Over the first 12 hours it was significantly lower in Black than White patients ($p \leq 0.05$).
- After a 4-week placebo washout period, HCTZ 50mg twice daily significantly reduced mean arterial BP (MABP) and the serum K^+ level for up to 36 weeks compared with placebo, in patients with essential hypertension (DBP >100mm Hg) on an unrestricted Na^+ diet.[16] There was a significant decrease in MABP after 1 week of treatment (from 117.2mm Hg during placebo washout to 110.5mm Hg; n = 13), sustained for up to 36 weeks (101.4mm Hg; n = 9) [$p < 0.01$ for both comparisons]. Serum K^+ levels were significantly reduced at week 1 (from 4 mmol/L during placebo washout to 3.0 mmol/L; $p < 0.001$) through to week 36 (3.2 mmol/L; $p < 0.001$). There was no significant change in Na^+ excretion during long-term treatment.
- In responders (defined as those with a >10% decrease in MABP, n = 7), cardiac output and stroke volume decreased significantly with HCTZ at weeks 4 and 12, compared with during placebo washout ($p < 0.05$), but the difference after this was not significant, as cardiac output increased to pre-treatment levels.[16] Across the whole study group, there was a transient increase in plasma renin at weeks 1 and 12 (from 76.5 μU/mL for placebo washout to 219.6 and 196.8; $p < 0.001$ for both comparisons), but by week 36 this was no longer significant in responders (69.0 μU/mL during placebo washout vs 151.7 μU/mL).[16]
- Intra-arterial HCTZ 25 and 75 μg/min/dL significantly (p value not stated) increased forearm blood

flow in six normotensive volunteers (BP 125/67mm Hg), indicating that HCTZ directly affects vasodilation in humans.[17] This effect was not significant in hypertensive patients (mean BP 162/95mm Hg). There was significant attenuation of HCTZ-mediated vasodilation when intra-arterial HCTZ 1 μg/min/dL was administered to normotensive subjects after intra-arterial tetraethylammonium, a selective blocker of calcium-activated K^+ (K_{Ca}) channels in arterial smooth muscle ($p < 0.02$). This supports a K^+ channel mediation of the vasodilatory effect of HCTZ.[17]

- The vasoconstrictive effect of intra-arterial noradrenaline (norepinephrine), which is attenuated by long-term HCTZ, was not inhibited by acute local infusion of intra-arterial HCTZ 1 μg/min/dL in six normotensive volunteers, suggesting there is no direct interaction of HCTZ with noradrenaline α-receptors.[17] However, an *in vitro* study evaluating acetazolamide, benzolamide, ethoxzolamide, HCTZ and bendroflumethiazide in guinea-pig mesenteric arteries demonstrated that in arteries pre-treated with noradrenaline, HCTZ 30 μmol/L relaxed the arteries ($p < 0.001$).[18] Charybdotoxin, which selectively inhibits K_{Ca} channels, abolished this effect ($p < 0.001$), further confirming the role of the K^+ channel.
- The vasorelaxant effect was associated with a rise in pH (quantitative data not reported, $p < 0.01$) only in the carbonic anhydrase-inhibiting thiazides tested (HCTZ and acetazolamide). This suggests that inhibition of carbonic anhydrase and consequent rise in pH are associated with K^+ channel activation. Bendroflumethiazide, which shows virtually no inhibition of carbonic anhydrase, had very little vasorelaxant effect, and it was not associated with a rise in pH.[18]

Telmisartan/HCTZ

- After 5 days of treatment in spontaneously hypertensive rats, a combination of telmisartan/HCTZ 3/10 mg/kg produced greater reductions in trough DBP, SBP and MABP (−44, −60 and −53mm Hg, respectively) than vehicle or telmisartan or HCTZ monotherapy (−31, −39 and −36 mm Hg, respectively, for telmisartan monotherapy, results shown graphically for HCTZ monotherapy and vehicle; $p < 0.05$ for all comparisons vs combined therapy).[19] Telmisartan/HCTZ, but neither monotherapy, resulted in a statistically significant increase in heart rate of up to 12 bpm from a baseline 299 bpm ($p < 0.05$ vs vehicle). The combined therapy also promoted renal water and electrolyte excretion compared with vehicle ($p < 0.01$) but some attenuation (not statistically significant) of urinary K^+ loss associated with HCTZ was observed with telmisartan/HCTZ (396.0 μmol/100g vs 422.0 μmol/100g for HCTZ and 331.3 μmol/100g for vehicle).
- Studies on the antihypertensive effects of combined telmisartan/HCTZ in obese patients with type 2 diabetes mellitus and in elderly patients are ongoing.[13]

2. Pharmacokinetic Profile

The pharmacokinetics of telmisartan and HCTZ are not altered when the two drugs are administered together.[20] The profiles of the two drugs are therefore reported separately, with one study in which both drugs were administered concurrently reported last.

Telmisartan

- Telmisartan is rapidly absorbed, with a mean maximum plasma concentration (C_{max}) of 44.7 ng/mL occurring between 0.5 and 1 hour (t_{max}) after a single [^{14}C]-radiolabelled 40mg dose in five healthy male volunteers.[21] In two concurrent studies,[22] patients with hypertension receiving telmisartan 40 mg/day achieved a mean C_{max} of 88.2 ng/mL at a median t_{max} of 1.5 hours on day 7 ($n = 6$) and a mean C_{max} of 130 ng/mL (steady state) at a median t_{max} of 1 hour on day 28 ($n = 40$). After 28 days of telmisartan 80 mg/day, mean C_{max} was 465 ng/mL and also occurred at a median t_{max} of 1.0 hour ($n = 41$).[22] Bioavailability of a 40mg oral dose is 42–43%.[21,22]
- Steady state was reached by day 7 in two 4-week trials in patients with hypertension treated with telmisartan 40, 80 or 120 mg/day ($n = 121$) or telmisartan 20–160 mg/day ($n = 227$).[22,23] In

healthy volunteers, the mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) after a single dose of telmisartan 40mg was 491 ng • h/mL.[21] In patients with hypertension, after 28 days, mean AUC_∞ values were 1304 ng • h/mL (40 mg/day) and 2651 ng • h/mL (80 mg/day).[22]

• Telmisartan is almost totally plasma protein bound, with a mean unbound percentage of ≈0.5%.[21,24] Most of the telmisartan dose remains as parent compound, with glucuronidation occurring at first pass in the intestinal wall and liver.[21] One hour after a single dose of telmisartan 40mg, 10.9% of the drug was present as telmisartan glucuronide. Total body clearance was between 800 and 970 mL/min (48–58.2 L/h) in healthy volunteers.[22,25]

• In 227 patients with hypertension, telmisartan (20–160 mg/day for 4 weeks) had a mean elimination half-life ($t_{1/2}$) of approximately 24 hours.[23] In healthy volunteers, telmisartan was slowly eliminated, with 98% excreted in faeces, 90% of this within 120 hours, and less than 1% eventually excreted through the kidneys.[21]

HCTZ

• In two studies in healthy volunteers, the absorption of HCTZ was similar after a single dose of HCTZ 25mg.[14,26] Mean C_{max} values were 127 ng/mL (n = 12)[26] and 142 ng/mL (n = 8)[14] and were attained after 2.4 and 2–5 hours respectively, with mean AUC_{36h} of 978 ng • h/mL.[26] The bioavailability of HCTZ 25–50mg doses, based on urinary recovery, was 54–75%,[26,27] similar to the 84% urinary recovery when HCTZ 25mg was administered to 13 volunteers with telmisartan 160mg.[20] In eight healthy volunteers, after a single HCTZ 12.5mg dose, mean C_{max} was 70 ng/mL at a t_{max} of 1.5–4 hours and AUC_{9h} averaged 351 ng • h/mL.[14]

• Elimination of HCTZ is biphasic, with a $t_{1/2}$ of ≈9 hours (range of slower phase 5.6–14.8 hours).[14,20,27,28] HCTZ is eliminated mainly through the kidneys.[14,26]

Telmisartan/HCTZ

• Thirteen healthy volunteers all received telmisartan 160 mg/day, HCTZ 25 mg/day and telmisartan/HCTZ 160/25 mg/day for 7 days each, separated by 14-day washout periods, in an open-label crossover study.[20] A 25mg dose of HCTZ administered with telmisartan reached a mean C_{max} of 159.6 ng/mL after a mean 2.3 hours, not significantly different from the mean C_{max} of HCTZ alone (170.0 ng/mL) reached after a mean 2.4 hours. When administered with telmisartan, the median HCTZ $t_{1/2}$ was 9.4 hours and 84.2% was excreted in urine over 24 hours, compared with 9.9 hours and 80.5% when administered alone. For telmisartan administered with HCTZ, a geometric mean C_{max} of 1315 ng/mL was reached after 0.9 hours, with a mean $t_{1/2}$ of 22 hours.[20]

Special Patient Populations

• In 12 normotensive elderly patients (mean age 70 years), telmisartan C_{max} and AUC were similar to those of younger individuals, and terminal $t_{1/2}$ at steady state was 36.4–37.2 hours (20–120mg dose).[22] Geometric mean C_{max} in six elderly women receiving telmisartan 120 mg/day for 7 days was more than three times higher than in six elderly men. The increased exposure in elderly women was not considered clinically relevant and no change in dose was recommended.

• The effect of renal function on HCTZ was assessed in patients with normal, mildly impaired and moderately to severely impaired renal function (creatinine clearance [CL_{CR}] ≥100 mL/min [≥5.9 L/h], 31–99 mL/min [1.9–5.9 L/h] and ≤30 mL/min [≤1.8 L/h]; n = 6, 10 and 7 respectively), who received HCTZ 50mg after a 3-day period without diuretics.[29] The $t_{1/2}$ of HCTZ increased significantly from a mean 6.4 hours in patients with normal renal function to 11.5 and 20.7 hours, respectively, in patients with mild and moderate to severe renal impairment ($p < 0.01$ for both comparisons).

• Renal clearance of HCTZ significantly decreased from 285 mL/min (17.1 L/h) to 75 and 17 mL/min (4.5 and 1.0 L/h), respectively, $p < 0.001$ for both

comparisons. Only about 10% of HCTZ was recovered in the urine of pre-uraemic patients. Reduction to half the normal dosage of HCTZ was suggested for patients with CL_{CR} of 30–90 mL/min (1.8–5.4 L/h).[29] Telmisartan/HCTZ is not recommended in patients with CL_{CR} ≤30 mL/min (≤1.8 L/h).[30]

- In six patients with severe renal insufficiency (mean interdialysis serum creatinine 662 μmol/L), AUC_{24h} and C_{max} after a single dose of telmisartan 120mg were markedly reduced, whether telmisartan was administered between dialyses (511 ng • h/mL and 100 ng/mL), or during dialysis (667 ng • h/mL and 169 ng/mL), compared with those in 12 healthy volunteers (1940 ng • h/mL and 438 ng/mL).[31] The t_{max} was unaffected. Absorption, based on AUC, was estimated at ≈25% of that in healthy volunteers, although the free fraction of the drug increased by 100% because of a small percentage reduction in protein binding. The BP-lowering effect of telmisartan 40–80mg is not altered in patients with mild to moderate renal failure and dosage increases are not recommended.[32]

- Hepatic impairment (Child-Pugh score 6–9) affected the absorption of telmisartan in 12 patients who received single doses of 20 or 120mg, with each dose separated by a 14-day washout period.[24] C_{max} values increased 6.4- and 3.2-fold (20 and 120mg doses, respectively) and AUC_{∞} values increased 2.7- and 3.1-fold compared with those in healthy controls. Plasma protein binding was unaffected, as was t_{max}. Average bioavailability among patients with hepatic impairment was 97.2% and total clearance decreased to 412 mL/min (24.7 L/h) compared with 934 mL/min (56.0 L/h) in healthy subjects. It was suggested that low dosages of telmisartan be considered in these patients.[24]

- Seven patients admitted to hospital with congestive heart failure were given HCTZ 50 or 75mg after at least 24 hours without furosemide.[33] The t_{max} varied between 1.5 and 8 hours, and total urinary recovery of the drug over 6 days was 20.8–71.6%; in three patients it was below 40%. It was suggested that absorption may be delayed and decreased in these subjects. Although renal clearance was also low, the final urine samples contained no HCTZ, suggesting all absorbed drug had been eliminated and collected.

3. Therapeutic Efficacy

Large multicentre trials, including three randomised, double-blind trials of 8 weeks' duration[1,3,5] (n = 321–807), a 6-week, randomised, open-label, multicentre, blinded endpoint study of 591 patients[34] and two long-term, open-label extension studies (n = 483[35] and 884[2]), examined the use of once-daily telmisartan/HCTZ in patients aged ≥18 years with mild to moderate essential hypertension. Some studies used a fixed-dose formulation throughout the trial[1,3,5,34] and some extended earlier trials by adding HCTZ therapy to telmisartan monotherapy where needed, comparing these with telmisartan plus another antihypertensive with or without HCTZ,[2,35] or with other drugs.[36,37]

Two 26-week, randomised, double-blind, parallel-group studies started with monotherapy comparisons (telmisartan vs atenolol [n = 520][36] or enalapril [n = 272][37]) and included groups whose treatment was titrated to include HCTZ. The latter trial was conducted in elderly patients (aged ≥65 years with a mean age of 71 years).[37]

Mild to moderate hypertension was variously defined as seated trough BP of 140/90–200/114mm Hg after 8 weeks of telmisartan monotherapy,[3,5] seated BP of 140/95–200/114mm Hg after telmisartan monotherapy or losartan/HCTZ therapy,[35] mean 24-hour ambulatory DBP exceeding 85mm Hg and mean seated DBP 90–109mm Hg plus SBP <180mm Hg[34] or supine DBP of 95–114mm Hg during placebo run-in periods of 2–5 weeks, and supine SBP of either 140–200mm Hg just before randomisation,[1] or under 210[36] or 220mm Hg[37] at any time during the run-in phase.

Most trials had as their primary endpoint a reduction in DBP, either from baseline[1,3,5,37] or to <90mm Hg,[2,35] or both.[36] One[34] used the change over 6 weeks in ambulatory DBP over the last 6 hours of a 24-hour dosing interval as the primary efficacy parameter (this trial measured both ambulatory DBP and SBP over the last 6 and complete 24 hours of the dosing interval and also reported re-

sponder rates [DBP <90mm Hg or ≥10mm Hg decrease from baseline, SBP <140mm Hg or ≥10mm Hg decrease from baseline]). Two studies included supine SBP as a primary endpoint.[36,37] Most patients were Caucasian, with a mean age (excluding the trial in the elderly) of 53–58 years. Reported participant numbers reflect intention-to-treat figures.

Comparisons with Telmisartan Monotherapy

- Fixed-dose combinations of telmisartan/HCTZ reduced BP significantly more than telmisartan monotherapy in two randomised, double-blind, parallel-group studies of patients with an inadequate response to 4 or 8 weeks of telmisartan monotherapy ($p < 0.01$).[3,5] After 8 weeks, the reductions in mean seated DBP (primary endpoint) and mean seated SBP were significantly better in patients treated with telmisartan/HCTZ 40/12.5 or 80/12.5 mg/day than with telmisartan 40 mg/day or 40 mg/day titrated to 80 mg/day ($p < 0.01$ for all comparisons; figure 1).
- Seated trough BP was normalised (<140/90mm Hg) after 8 weeks in 51.6%[3] and 41.5%[5] of patients in the telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day groups, respectively, compared with 23.5% and 26.1% of those who continued with monotherapy ($p < 0.05$ for all comparisons). Compliance with telmisartan/HCTZ 80/12.5 mg/day was 98.9% and 98.8% with telmisartan 80 mg/day.[5]
- Telmisartan/HCTZ also proved more effective than either monotherapy in reducing supine DBP and SBP in another large trial.[1] Following a 4-week placebo run-in, patients (n = 807) underwent an 8-week trial period, with the study focusing on patients receiving telmisartan/HCTZ 80/12.5 mg/day or 40/12.5 mg/day relative to those randomised to telmisartan or HCTZ monotherapy or continued placebo. Telmisartan/HCTZ 80/12.5 mg/day achieved a significantly better reduction in both mean supine DBP (primary endpoint) and SBP than telmisartan or HCTZ monotherapy in this randomised, double-blind, parallel-group, multicentre, 4×5 factorial design study ($p < 0.01$ both comparisons; figure 2).

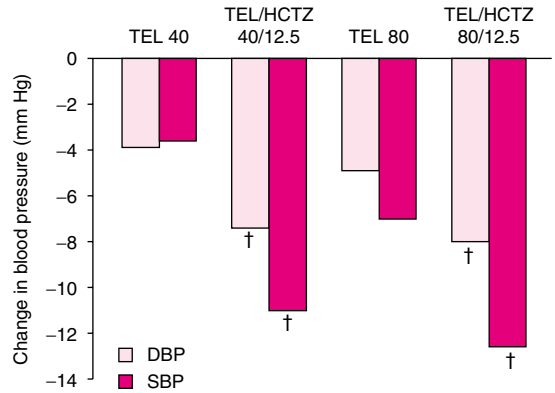

Fig. 1. Antihypertensive effects of telmisartan (TEL)/hydrochlorothiazide (HCTZ) therapy and TEL monotherapy in patients with mild to moderate essential hypertension. Reduction from baseline after 8 weeks in seated systolic blood pressure (SBP) and diastolic BP (DBP) in patients with an inadequate response to TEL monotherapy. In two randomised, double-blind, multicentre studies, patients received TEL 40 mg/day or TEL/HCTZ 40/12.5 mg/day (n = 321) [results estimated from graph];[3] or TEL 40 mg/day titrated to 80 mg/day or TEL/HCTZ 80/12.5 mg/day (n = 491).[5] † $p < 0.01$ vs TEL monotherapy.

- The reduction in supine SBP was significantly greater in patients treated with telmisartan/HCTZ 40/12.5 mg than in those treated with either monotherapy ($p < 0.01$ for both comparisons), but the reduction in supine DBP with this combination was not significantly greater than that with telmisartan 40 mg/day monotherapy (figure 2). Both dosages of telmisartan/HCTZ also resulted in significantly better reductions in standing DBP and SBP than the respective monotherapies, which in turn all produced greater reductions than placebo ($p \leq 0.01$ for all comparisons).[1]
- Separate results were reported for the subgroup of Black participants (n = 219) in this study,[38] with a significantly larger decrease in mean supine trough DBP from baseline with telmisartan/HCTZ 80/12.5 mg/day than with either telmisartan 80 mg/day or HCTZ 12.5 mg/day (−13.3 vs −4.6 and −5.2mm Hg reductions, respectively; $p < 0.01$ for both comparisons). Telmisartan/HCTZ 80/12.5 mg/day also resulted in a relative reduction in supine trough SBP of 21.5mm Hg, which was significantly greater than with telmisartan or HCTZ alone (−7.8 and −9.2mm Hg, respectively, $p < 0.01$ for both comparisons). Recipients of telmisartan/HCTZ 40/12.5 mg/day

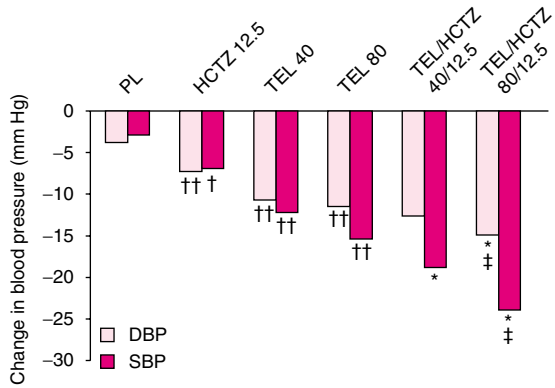

Fig. 2. Comparative antihypertensive effects of telmisartan (TEL)/hydrochlorothiazide (HCTZ) therapy and TEL or HCTZ monotherapy in patients with mild to moderate essential hypertension.[1] Reduction from baseline in supine trough systolic blood pressure (SBP) and supine trough diastolic BP (DBP) in patients with a BP of 140/95–200/114mm Hg. In this multicentre, randomised, double-blind, placebo-controlled, parallel-group study, patients (n = 807) received TEL 0–160 mg/day and/or HCTZ 0–25 mg/day, some thereby receiving monotherapy with either telmisartan or HCTZ or continued placebo (PL). The study focus was on two combinations: TEL/HCTZ 40/12.5 and 80/12.5 mg/day. Data for only these combinations, plus monotherapy and PL, are shown. * $p < 0.01$ vs both monotherapies; † $p < 0.05$, †† $p < 0.01$ vs PL; ‡ $p < 0.05$ vs TEL/HCTZ 40/12.5 mg/day.

achieved a significant reduction in supine trough SBP relative to telmisartan 40 mg/day monotherapy recipients (−14.3 vs −2mm Hg; $p \leq 0.01$) and in DBP versus HCTZ 12.5 mg/day monotherapy (−10 vs −5.2mm Hg) [$p \leq 0.05$ for both comparisons].

Comparison with Losartan/HCTZ

- Fixed-dose telmisartan/HCTZ significantly reduced mean ambulatory DBP and SBP over the last 6 hours of a 24-hour period compared with fixed-dose losartan/HCTZ.[34] In newly-diagnosed or inadequately treated patients with hypertension (n = 591) ambulatory DBP was reduced from baseline (24-hour mean ≥85mm Hg), by 9.7mm Hg in the losartan/HCTZ 50/12.5 mg/day group, compared with 11.4mm Hg and 12.1mm Hg in the telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day groups, respectively, over these 6 hours. Treatment differences were −1.8mm Hg ($p < 0.05$) and −2.5mm Hg ($p < 0.001$), respectively. Compared with losartan/HCTZ 50/12.5 mg/day, treatment differences for ambulatory SBP over the last 6 hours of a 24-hour period were also significant, at −2.5mm Hg ($p < 0.05$) for telmisartan/HCTZ 40/12.5 mg/day and −3.4mm Hg ($p < 0.01$) for telmisartan/HCTZ 80/12.5 mg/day.
- Relative to losartan/HCTZ 50/12.5 mg/day, over the whole 24-hour period, both dosages of telmisartan/HCTZ significantly reduced mean ambulatory SBP; telmisartan 80/12.5 mg/day also significantly reduced mean ambulatory DBP.[34] Treatment differences for ambulatory SBP were −2.1mm Hg ($p < 0.05$) and −3.4mm Hg ($p < 0.001$) for telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day compared with losartan/HCTZ 50/12.5 mg/day, respectively. For ambulatory DBP, the treatment difference was −2.3mm Hg for telmisartan/HCTZ 80/12.5 mg/day compared with losartan/HCTZ ($p < 0.001$). Responder rates for ambulatory DBP (69–77%) and SBP (79–82%) were similar across all treatment groups.
- At the end of the 6-week trial period, significant differences in patients treated with losartan/HCTZ 50/12.5 mg/day compared with telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day were also seen for reductions in seated trough (clinic) DBP and SBP.[34] Reductions in clinic DBP were 6.6mm Hg for losartan/HCTZ, compared with 9.7 and 10.0mm Hg for telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day, respectively ($p < 0.001$, both comparisons) and corresponding clinic DBP responder rates were 46% compared with 59% ($p < 0.013$) and 61% ($p < 0.004$). Clinic SBP decreased by 13.4mm Hg in recipients of losartan/HCTZ 50/12.5 mg/day and by 15.9mm Hg ($p < 0.05$) and 17.3mm Hg ($p < 0.001$)

in recipients of telmisartan/HCTZ 40/12.5 and 80/12.5 mg/day, respectively. The clinic SBP responder rate for losartan/HCTZ recipients was 65%, compared with respective rates of 76% ($p < 0.022$) and 78% ($p < 0.005$) for the telmisartan/HCTZ groups.

Comparison with Enalapril

- A 26-week randomised trial in 272 elderly patients with DBP 95–114mm Hg and SBP <220mm Hg compared the efficacy of telmisartan with enalapril, with HCTZ added after 12 or 16 weeks for those who had not achieved the secondary endpoint of reduction in supine trough DBP to <90mm Hg.[37] Following a 3- to 5-week placebo run-in, patients received telmisartan 20 mg/day or enalapril 5 mg/day, with dosages doubled after 4 and 8 weeks if required. If required, HCTZ 12.5 mg/day was added at week 12 to the maximal dose of telmisartan 80 mg/day or enalapril 20 mg/day, or at week 16 to any dose level, and increased to 25 mg/day if needed at any time during maintenance.
- After 26 weeks, the placebo-adjusted changes from baseline in supine trough SBP and DBP (primary endpoints) were −22.1 and −12.8mm Hg for the telmisartan with or without HCTZ group, and −20.1 and −11.4mm Hg for the enalapril with or without HCTZ group. In contrast, the changes at the end of the 12-week monotherapy period were −15.5 and −10.0mm Hg for telmisartan and −12.7 and −8.0mm Hg for enalapril.[37]
- By the end of the study, the primary endpoint of reduction of trough supine SBP by ≥10mm Hg was achieved in 67% of patients initially randomised to enalapril and 70% of those randomised to telmisartan, and the primary endpoint of reduction of trough supine DBP by 7–10mm Hg by 68% and 71%, respectively.[37] However, 38% and 36%, respectively, of these responders required HCTZ. Adding HCTZ, usually 12.5 mg/day, achieved the endpoint in 44% and 49% of non-responders to telmisartan and enalapril monotherapy, respectively.

Comparison with Atenolol

- In a 26-week double-blind, parallel-group, multicentre trial, 520 patients with morning mean supine DBP 95–114mm Hg and SBP <210mm Hg after a 2- to 3-week placebo run-in period were randomised in a 2 : 1 ratio to initial doses of telmisartan 40 mg/day or atenolol 50 mg/day, the primary efficacy endpoint being reduction in supine morning DBP to ≤90mm Hg and/or by ≥10mm Hg from baseline.[36] After 4 or 8 weeks, if supine DBP was >95mm Hg or had not reduced by ≥10mm Hg from baseline, dosages were doubled. A second titration at 8 weeks was performed; if baseline reduction in supine DBP was 7–10mm Hg, HCTZ 12.5 mg/day was added in both treatment groups, and for those receiving telmisartan, if supine DBP was >95mm Hg or baseline reduction <7mm Hg, telmisartan was increased to 120 mg/day. If after 16 weeks supine DBP was >90mm Hg in either group, HCTZ was either added (12.5 mg/day) or increased to 25 mg/day.
- At week 26, 84% and 78%, respectively, (difference not statistically significant) of patients initially randomised to telmisartan or atenolol had achieved the primary endpoint. Thirty two percent and 28% of these initially randomised to telmisartan and atenolol, respectively, were taking HCTZ (usually the lower 12.5 mg/day dosage [77% and 79% of these patients, respectively]). Mean supine DBP was reduced by an additional 6mm Hg when HCTZ was added to telmisartan and 3.5mm Hg when added to atenolol, giving overall mean supine DBP reduction with concomitant therapies of 11.6 and 8.3mm Hg, respectively. For those responsive to monotherapy, mostly at the lowest dosage, the mean reduction in supine DBP was 15.7mm Hg with telmisartan and 15.2mm Hg with atenolol.

Long-Term Efficacy

- In a 1-year, open-label, multicentre, extension study, 483 patients who had previously participated in a randomised 6-week trial comparing telmisartan 80 mg/day with losartan/HCTZ 50/12.5 mg/day, had their treatment titrated over the next year in accordance with achievement or otherwise of the primary endpoint of seated DBP <90mm Hg.[35] All patients in the extension study were initially treated with telmisartan 80 mg/day, then stepwise titration at 4-week intervals to one of four levels occurred as

needed: continuation of telmisartan 80 mg/day, move to telmisartan/HCTZ 80/12.5 mg/day, then increase telmisartan/HCTZ dosage to 80/25 mg/day, and if the response was still inadequate, move to telmisartan plus another antihypertensive with or without HCTZ (58%, 17.5%, 17.5% and 7% of patients, respectively, at study end).

- The primary endpoint, DBP control, was achieved by 70% of patients in the telmisartan monotherapy group and by 55.8%, 54.7% and 64.7% of the patients receiving telmisartan/HCTZ 80/12.5 mg/day, 80/25 mg/day or telmisartan 80 mg/day plus another antihypertensives with or without the HCTZ.[35] The mean reduction in seated DBP was 2.8mm Hg with telmisartan monotherapy, compared with 4.7, 6.2 and 12.8mm Hg, respectively, for the other groups; reductions in seated SBP were 2.7, 5.9, 10.5 and 16.9mm Hg, respectively. Across all groups, the reductions in seated DBP and SBP from the start of the preceding study to the end of the extension study were similar (14.0–16.4mm Hg and 21.5–25.3mm Hg). The antihypertensive effects of telmisartan with or without other agents was sustained throughout the extension phase, with response rates of 83%, 74.4%, 81.4% and 73.5%, respectively, in the four groups.

- In a 4-year multicentre, open-label extension study,[2] 888 patients who had participated in one of four 8- or 26-week telmisartan trials chose to continue in a follow-up trial assessing the efficacy of telmisartan monotherapy (40 or 80 mg/day) with, if required, the addition of HCTZ (12.5 or 25 mg/day) and subsequently one or more other antihypertensives, excluding other angiotensin II antagonists, (± HCTZ) in achieving a primary endpoint of supine DBP <90mm Hg (BP control). Almost 80% of the patients (701), completed the trial with a median exposure of more than 3 years (1184 days).

- Although 90% of patients initially achieved DBP control after 8 weeks of telmisartan 40 or 80 mg/day monotherapy, this percentage dropped to 83% by week 12, 73% after 1 year, 65% after 2 years and 59% after 3 years, indicating that about one-third of patients who were initially responsive to monotherapy required additional therapy over time.[2] Adding HCTZ 12.5 mg/day in non-responders resulted in BP control in a further 9% of all patients by week 12, 11% by year 1, 13% by year 2 and 11% by year 3. Increasing the HCTZ dosage to 25 mg/day achieved the primary endpoint in a further 11% of patients by the end of year 1, 15% by year 2 and 14% by the end of year 3, so that 25% of all patients, equivalent to the majority (about 75%) of those whose initial response to monotherapy had declined by the end of year 3, were responsive to combined telmisartan/HCTZ.[2]

- During the study, 23.3% of patients had moved on to combined telmisartan/HCTZ (telmisartan 40 or 80 mg/day plus HCTZ 12.5 or 25 mg/day), 65.1% continued to receive telmisartan monotherapy (40 or 80 mg/day) and the remaining 11.6% of patients were treated with telmisartan plus another antihypertensive with or without HCTZ.[2]

Special Patient Populations

- In a subset of 35 elderly patients in a randomised, double-blind, placebo-controlled, factorial trial, the reduction in BP in recipients of telmisartan/HCTZ was approximately twice that of recipients of HCTZ alone.[39] The reduction from baseline in supine SBP was 12.4mm Hg with HCTZ 12.5 mg/day (n = 13), compared with 16.3 and 25.3mm Hg for recipients of telmisartan (n = 8) and telmisartan/HCTZ (n = 14), respectively; these reductions were not significantly different to those in younger patients (5.8, 15.3 and 23.5mm Hg, respectively).[39]

- In 188 patients with diabetes (type not specified), included in a pooled analysis of randomised, controlled trials the mean reductions in seated trough clinic DBP and SBP in recipients of telmisartan/HCTZ 80/12.5 mg/day, after a mean treatment period of 148 days, were 12.6 and 26.1mm Hg, respectively.[39] After a mean treatment period of 115.7 days, the mean reductions with telmisartan 80 mg/day monotherapy were 9.4 and 15.9mm Hg, respectively (p value not stated).

4. Tolerability

- Telmisartan/HCTZ was well tolerated in the clinical trials reviewed in section 3.[1-3,5,35-37,40] This is

consistent with a meta-analysis of 9574 patients[41] that found the incidence of treatment-related adverse events to be similar in recipients of placebo (n = 819), telmisartan 20–160 mg/day alone (n = 6575), or telmisartan/HCTZ 10–160/6.25–25 mg/day (n = 2180) [incidences of 10.5%, 12% and 12.8% of patients, respectively].

- The incidence of treatment-related adverse events per patient per treatment year was higher in placebo recipients (1.02) than in recipients of telmisartan monotherapy (0.20) or combined telmisartan/HCTZ therapy (0.18).[41] The incidence of 'all-cause' adverse events was greater in the patients receiving active treatment (52% for telmisartan and 59.5% for telmisartan/HCTZ vs 38.2% for placebo). Serious adverse events occurred more frequently in telmisartan/HCTZ recipients (5.6% vs 1.1% for placebo and 4.3% for telmisartan monotherapy) but per patient per treatment year, the incidence was similar at 0.08 for placebo, 0.08 for telmisartan/HCTZ recipients and 0.07 for telmisartan monotherapy recipients (statistical analysis not reported).[41]

- Adverse events from any cause, affecting ≥2% of patients in any treatment group in the largest, double-blind study in monotherapy, combined therapy and placebo recipients are shown in figure 3.[1] As indicated, some common adverse events, such as headache, affected more patients in the placebo than the active treatment groups (no p value stated). Other double-blind, randomised studies evaluating telmisartan/HCTZ treatment have reported headache, dizziness, fatigue, upper respiratory tract infections and urinary tract infections affecting ≥ 2% of patients in the combined therapy groups;[3,5] only dizziness and upper respiratory tract infections affected more than 5% of recipients of telmisartan/HCTZ combined therapy.[3,5]

- Two studies reported diarrhoea, one finding the incidence significantly higher in patients receiving combined telmisartan/HCTZ therapy (4.1% of patients vs 0.0% on monotherapy, p = 0.002)[5] and one finding the incidence higher in patients receiving telmisartan monotherapy (5.3% telmisartan vs 3.4% telmisartan/HCTZ, no p value stated).[1] Some studies reported oedema, believed to be drug-related and affecting ≥2% of patients receiving telmisartan 80 mg/day and telmisartan/HCTZ 40/12.5 mg/day, but not 80/12.5 mg/day.[1,3,5] One case of suspected angioedema in a woman receiving telmisartan 160 mg/day was reported.[1]

- In a 4-year extension trial,[2] more mild to moderate adverse events were reported in the recipients of telmisartan and telmisartan/HCTZ (84.8% and 87.8%) than in those titrated to telmisartan 80mg plus one or more other antihypertensives with or without HCTZ (35.9%), but relative treatment periods averaged 790, 738 and 82 days, respectively (no statistical analysis). The incidence of potentially drug-related adverse events was similar with telmisartan monotherapy (15.1%) and combined telmisartan/HCTZ therapy (14.8%) although there was a lower incidence in the group with the shortest duration of treatment, recipients of telmisartan plus another antihypertensive with or without HCTZ (2.9%).

- In the same trial, serious adverse events considered to be drug-related occurred in 8 of 884 (0.9%) patients.[2] Six of these events occurred in patients taking combined telmisartan/HCTZ (atrial fibrillation, tachycardia and angina pectoris in the telmisartan/HCTZ 80/12.5 mg/day group and palpitation with chest pain, haematemesis and pain in the telmisartan/HCTZ 80/25 mg/day group), compared with two cases of hypotension/dizziness in the telmisartan 40 mg/day monotherapy group.

- Elderly patients[37] generally tolerated telmisartan with or without HCTZ well, with 25% of patients experiencing an adverse event considered to be treatment-related, compared with 37% of those receiving enalapril with or without HCTZ, over the 29- to 31-week study period. The addition of HCTZ did not appear to affect the telmisartan tolerability profile; specific events were mostly not separately reported for telmisartan and telmisartan/HCTZ. The most common events in those taking telmisartan with or without HCTZ were coughing (6.5% vs 15.8% in the enalapril group), diarrhoea, dizziness and headache.

- A subgroup analysis (n = 118) in one trial[38] showed that the incidence of adverse events in Black

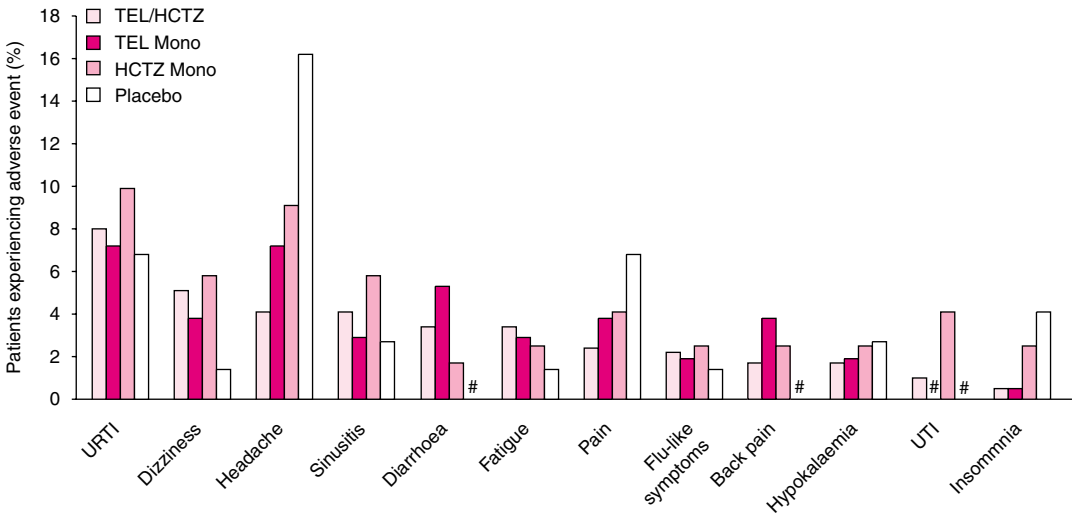

Fig. 3. Comparative tolerability profile of telmisartan (TEL)/hydrochlorothiazide (HCTZ) in patients with mild to moderate essential hypertension. Patients received TEL 20–160 mg/day or HCTZ 6.25–25 mg/day monotherapy (Mono), TEL/HCTZ 20/6.25–160/25 mg/day combined therapy or placebo. Adverse events from any cause with incidence of ≥2% in any of the specified treatment groups, in an 8-week, randomised, double-blind, placebo-controlled, multicentre study (n = 807). **URTI** = upper respiratory tract infection; **UTI** = urinary tract infection; # = incidence in patient group of 0%.[1]

patients receiving telmisartan/HCTZ 40/12.5 or 80/12.5 mg/day (n = 16 and 22), at 37.5% and 63.6%, respectively, was similar to that in the overall trial population.

- Hypokalaemia was reported in 4 of 414 (1.0%) patients treated with telmisartan/HCTZ in one parallel-group study compared with 5 of 121 (4.1%) patients taking HCTZ monotherapy.[1] The potassium loss often associated with HCTZ monotherapy[14] was reduced in patients treated with the telmisartan/HCTZ combinations. Only one patient with hypokalaemia, receiving telmisartan/HCTZ 80/12.5 mg/day, was Black.[38] A meta-analysis reported hypokalaemia occurring in 0.3% of patients treated with telmisartan/HCTZ combinations, with a similar incidence of hyperuricaemia (0.23%).[41]

5. Dosage and Administration

In the EU, telmisartan/HCTZ 40/12.5mg or 80/12.5mg once daily is indicated for use in patients with essential hypertension who have not responded to monotherapy with telmisartan 40 or 80 mg/day, respectively.[42] In the US, telmisartan/HCTZ 80/12.5mg once daily is indicated in patients who have not responded to monotherapy with telmisartan 80 mg/day or HCTZ 12.5 mg/day or who experience hypokalaemia with HCTZ 25 mg/day.[30] In the US, the dosage may be titrated up to a maximum of telmisartan/HCTZ 160/25 mg/day if required.

6. Telmisartan/Hydrochlorothiazide: Current Status

Telmisartan/HCTZ is approved in the US and EU as second-line therapy for the treatment of essential hypertension in patients whose BP is not adequately controlled on monotherapy, or (US only) who experience hypokalaemia with HCTZ monotherapy. Large, well controlled, short- and long-term clinical trials have shown improved efficacy with telmisartan/HCTZ versus both HCTZ and telmisartan monotherapy. Telmisartan/HCTZ was generally well tolerated and was associated with good compliance.

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