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Telmisartan/Hydrochlorothiazide

A Review of its Use as Fixed-Dose Combinations in Essential Hypertension

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Data Selection

Sources: Medical literature published in any language since 1980 on telmisartan/hydrochlorothiazide, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Heath | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'telmisartan hydrochlorothiazide'. Searches were last updated 8 August 2008.

Selection: Studies in patients with hypertension who received telmisartan/hydrochlorothiazide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Telmisartan, hydrochlorothiazide, hypertension, fixed-dose combination, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, dosage and administration.

Contents

Summary

Abstract

Fixed-dose combinations of telmisartan and hydrochlorothiazide (HCTZ) [Micardis Plus®, Micardis® HCT, PritorPlus®] are available in many countries for the treatment of patients with essential hypertension. Combining the angiotensin II receptor antagonist (angiotensin II receptor blocker [ARB]) telmisartan with the thiazide diuretic HCTZ provides antihypertensive therapy with complementary mechanisms of action. In the US and EU, telmisartan/HCTZ is approved for patients whose hypertension is not adequately controlled with telmisartan monotherapy; US labelling for the fixed-dose combination also includes inadequate control of blood pressure (BP) with HCTZ monotherapy.

The antihypertensive efficacy of once-daily telmisartan/HCTZ has been demonstrated in several large, randomized trials in patients with stages 1 and 2 hypertension. The addition of HCTZ to telmisartan achieved significant reductions in BP in nonresponders to telmisartan monotherapy, and the antihypertensive efficacy of telmisartan/HCTZ was similar to or significantly greater than that of various comparator agents. Moreover, in studies that used ambulatory BP monitoring, telmisartan/HCTZ provided consistent 24-hour BP reductions throughout morning, daytime and night-time periods. The BP-lowering efficacy over the entire 24-hour dose administration interval is consistent with the pharmacokinetic profile of telmisartan, which has the longest elimination half-life among currently available ARBs and a unique chemical structure. Adverse events with telmisartan/HCTZ in clinical trials were typically mild and transient, and no unexpected events occurred that had not been previously reported with either telmisartan or HCTZ. Extensive tolerability data are available for telmisartan, in particular from the ONTARGET study, the largest clinical outcomes trial with an ARB. As such, fixed-dose combinations of telmisartan/HCTZ provide an effective, rational and generally well tolerated treatment option for the management of patients with hypertension.

Pharmacological Properties

Fixed-dose combinations of telmisartan/HCTZ comprise two antihypertensive agents with complementary mechanisms of action. The ARB telmisartan selectively blocks the binding of angiotensin II to the angiotensin II type 1 (AT_1) receptor in various tissues, thereby inhibiting angiotensin II-induced vasoconstriction and aldosterone secretion. HCTZ is a thiazide diuretic that acts on renal tubular mechanisms of electrolyte reabsorption, leading to reductions in extracellular fluid volume and peripheral resistance.

The pharmacokinetic properties of telmisartan and HCTZ are unaffected when the two drugs are administered concurrently, and the pharmacokinetic profiles of each agent administered alone are well defined. Telmisartan achieves maximum plasma concentrations (C_{max}) 0.5–1.5 hours after oral administration, has a volume of distribution (V_d) of 500 L, is highly bound to plasma protein (>99.5%) and has an elimination half-life ($t_{1/2}$) of >20 hours, which is longer than that of other ARBs. Telmisartan is primarily eliminated in the faeces via biliary excretion. HCTZ reaches C_{max} ≈1–3 hours after oral administration, is 68% bound to plasma protein, has a V_d of 0.83–1.14 L/kg, a $t_{1/2}$ of 10–15 hours and is eliminated almost entirely as unchanged drug in the urine.

Therapeutic Efficacy

The antihypertensive efficacy of once-daily telmisartan/HCTZ has been demonstrated in several large, well designed clinical trials in patients with mild to moderate hypertension. In two randomized, double-blind trials, the addition of HCTZ 12.5 mg/day to telmisartan 40 or 80 mg/day for 8 weeks in nonresponders to telmisartan monotherapy achieved significant reductions in mean trough seated diastolic BP (DBP) [primary endpoint] and systolic BP (SBP), as well as a higher response rate (SBP/DBP <140/90 mmHg), compared with continued treatment with telmisartan alone. Data from the phase IV MICCAT2 trial also showed that the use of telmisartan/HCTZ in nonresponders to telmisartan monotherapy was associated with additional BP-lowering efficacy and attainment of BP goals in the community practice setting.

Both telmisartan/HCTZ 80 mg/25 mg and valsartan/HCTZ 160 mg/25 mg once daily for 8 weeks produced marked reductions in BP compared with placebo in two randomized, double-blind trials in patients with stage 1 or 2 hypertension; however, significantly greater adjusted reductions in mean seated trough DBP and SBP (primary endpoint) were observed among patients in the telmisartan/HCTZ 80 mg/25 mg group than in the valsartan/HCTZ 160 mg/25 mg group. In randomized, open-label (blinded-endpoint) trials, once-daily telmisartan/HCTZ 80 mg/12.5 mg achieved significantly greater effects on early morning ambulatory and 24-hour BP than valsartan/HCTZ 160 mg/12.5 mg, and telmisartan/HCTZ 40 mg/12.5 mg and 80 mg/12.5 mg were associated with significantly greater reductions in early morning ambulatory DBP than losartan/HCTZ 50 mg/12.5 mg.

Three randomized, open-label (blinded-endpoint) trials compared the antihypertensive efficacy of telmisartan/HCTZ 80 mg/12.5 mg and agents other than ARBs administered once daily for 12–24 weeks. Results showed that, although all active treatments produced significant reductions in ambulatory BP compared with baseline, between-group reductions in BP (for 24-hour, daytime and nighttime SBP and DBP) were significantly greater for telmisartan/HCTZ 80 mg/12.5 mg compared with lisinopril/HCTZ 20 mg/12.5 mg in elderly hypertensive patients and compared with nifedipine gastrointestinal therapeutic system 60 mg

in adult hypertensive patients. Telmisartan/HCTZ 80 mg/12.5 mg was noninferior to amlodipine/HCTZ 10 mg/12.5 mg in older patients with predominantly systolic hypertension, although some statistical advantages favouring telmisartan/HCTZ (for 24-hour, daytime and morning SBP) were noted.

Tolerability

No unexpected adverse events have been reported in clinical trials with fixed-dose combinations of telmisartan/HCTZ that had not been previously reported with the individual drugs. The most commonly reported adverse events with telmisartan/HCTZ (incidence ≥2%) that occurred at a greater rate than with placebo (statistical analysis not reported) in clinical trials included upper respiratory tract infection, dizziness, sinusitis, diarrhoea, fatigue, influenza-like symptoms and nausea.

The incidence of adverse events with telmisartan/HCTZ was broadly similar to that with telmisartan monotherapy or with ARBs in combination with HCTZ in large comparative trials. However, telmisartan/HCTZ was associated with a markedly lower incidence of peripheral oedema than amlodipine/HCTZ in a large, randomized trial in elderly patients with predominantly systolic hypertension. Adverse events with telmisartan/HCTZ in clinical trials were typically mild and transient. Extensive tolerability data for telmisartan are also available from ONTARGET, the largest clinical outcomes trial conducted with an ARB.

1. Introduction

Globally, an estimated 1 billion people have hypertension,[1] including approximately 50–65 million in the US.[1,2] Moreover, the prevalence of hypertension in European countries may be substantially higher than that in the US.[3] Data from national surveys and other sources suggest a high prevalence of uncontrolled hypertension, with up to two-thirds of individuals with hypertension being inadequately treated.[4,5] Patients with poorly controlled hypertension are at increased risk of cardiovascular disease events, including myocardial infarction, heart failure, stroke and kidney disease.[1,6] Conversely, good control of blood pressure (BP) is associated with substantial reductions in cardiovascular disease events.[7-10]

Most patients with hypertension will require combination therapy with at least two antihypertensive drugs in order to achieve BP goals advocated in international guidelines.[1,6] BP targets are <140/90 mmHg in patients with uncomplicated hypertension and <130/80 mmHg in those with diabetes mellitus or other complications such as chronic kidney disease, stroke or myocardial infarction.[1,6]

Thiazide diuretics, alone or in combination with other antihypertensive agents, are recommended in treatment guidelines as initial therapy for most patients with hypertension.[1,6] When monotherapy does not provide adequate control of BP, the combination of a thiazide diuretic, such as hydrochlorothiazide (HCTZ), and an angiotensin II receptor antagonist (angiotensin II receptor blocker [ARB]), such as telmisartan, is a rational treatment option because they have complementary mechanisms of action, effectively reduce BP and are generally well tolerated when used together.[11-13] Moreover, thiazide diuretics[14] and ARBs[15,16] have both been shown to have beneficial effects on major clinical outcomes in patients with hypertension.

Fixed-dose combinations of telmisartan/HCTZ (Micardis Plus®, Micardis® HCT, PritorPlus®)[1] are available for once-daily oral administration in patients with essential hypertension that is not adequately controlled by telmisartan monotherapy (US[17] and EU[18] labelling) or HCTZ monotherapy (US labelling).[17] This article provides a brief overview of the pharmacological properties of telmis-

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

artan/HCTZ and reviews the clinical trial data for combinations of these antihypertensive agents.

2. Pharmacological Properties

2.1 Pharmacodynamic Properties

Fixed-dose combinations of telmisartan, an ARB that acts selectively on the angiotensin II receptor subtype 1 (AT_1), and HCTZ, a thiazide diuretic, provide antihypertensive therapies with complementary mechanisms of action.[11,17,18] By selectively blocking the binding of angiotensin II to the AT_1 receptor in various tissues, telmisartan inhibits vasoconstriction and aldosterone secretion associated with angiotensin II, the main pressor agent of the renin-angiotensin system (RAS). Thiazide diuretics act on renal tubular mechanisms of electrolyte reabsorption, increasing urinary sodium excretion, and indirectly reducing extracellular fluid volume and peripheral resistance, which, in turn, activates the RAS and increases the loss of urinary potassium via increased aldosterone secretion.[11,17,18] Coadministration of an ARB tends to reverse the potassium loss associated with thiazide diuretics,[11,17,18] and thiazide-induced RAS activation may increase the sensitivity of the AT_1 receptor, thereby enhancing the response to ARBs.[11]

The individual pharmacodynamic properties of telmisartan and HCTZ have been reviewed previously in some detail.[19,20] Pharmacodynamic data on the combined administration of telmisartan and HCTZ appear to be limited.

One study evaluated haemodynamic and metabolic changes in spontaneously hypertensive rats.[21] Rats that received telmisartan 3 mg/kg plus HCTZ 10 mg/kg orally for 5 consecutive days had significantly greater reductions in mean trough diastolic and systolic BP (DBP and SBP) and mean arterial BP than rats that received vehicle or telmisartan or HCTZ alone at the same dosage. Compared with vehicle, the combination of telmisartan plus HCTZ also significantly increased mean heart rate, and promoted renal water and electrolyte excretion.

Two clinical trials (discussed in section 3.3) comparing the BP-lowering effects of telmisartan/HCTZ with those of nifedipine gastrointestinal therapeutic system (GITS)[22] and lisinopril/HCTZ[23] also evaluated various pharmacodynamic effects of the drugs, such as sympathetic activation and changes in cognitive function. In the comparison with the calcium channel antagonist, 124 patients with mild to moderate hypertension were randomized to receive telmisartan/HCTZ 80 mg/12.5 mg once daily or nifedipine GITS 60 mg once daily for 12 weeks.[22] As well as providing more sustained and consistent reductions in BP (section 3.3), telmisartan/HCTZ was not associated with sympathetic activation, whereas nifedipine GITS was associated with a 20% increase from baseline in plasma noradrenaline levels at rest ($p < 0.05$ for between-group comparison). The other trial included 160 elderly (aged 61–75 years) patients with mild to moderate hypertension who were randomized to receive telmisartan/HCTZ 80 mg/12.5 mg once daily or lisinopril/HCTZ 20 mg/12.5 mg once daily for 24 weeks.[23] Telmisartan/HCTZ was associated with slightly greater reductions in ambulatory BP (section 3.3) and significantly ($p < 0.05$) improved 12- and 24-week scores on three of the six tests used to evaluate cognitive function (word-list memory, word-list recall and Trails B), whereas lisinopril/HCTZ did not improve any of the cognitive function scores.

2.2 Pharmacokinetic Properties

There are no published pharmacokinetic data for the fixed-dose combination of telmisartan/HCTZ; however, a crossover study in healthy volunteers showed that the pharmacokinetics of telmisartan and HCTZ are not altered when the two drugs are administered concurrently.[24] The pharmacokinetic properties of telmisartan and HCTZ, when administered as monotherapy, are well defined,[17-20] and a brief overview of the pharmacokinetic profiles of these drugs is presented in the following subsections and is summarized in table I. A notable feature of the pharmacokinetic profile of telmisartan is that its elimination half-life ($t_{1/2}$) [>20 hours] is longer than that of other ARBs.[25,26] Telmisartan also has a relatively high volume of distribution (table I) and

Table I. Overview of the pharmacokinetic profiles of telmisartan and hydrochlorothiazide (HCTZ) following oral administration in adults.[a] Data derived from EU summary of product characteristics[18] [b]

Parameter	Telmisartan	HCTZ
t_{max} (h)	0.5–1.5	≈1–3
F (%)	42 (40 mg); 58 (160 mg)	≈60
C_{max}	Non-linear (greater than proportional ↑ with increasing doses[c])	NR
AUC	Non-linear (greater than proportional ↑ with increasing doses[c])	NR
Plasma protein binding (%)	>99.5	68
V_d	≈500 L	0.83–1.14 L/kg
$t_{½}$ (h)	>20	10–15
CL or CL_R (mL/min)	>1500 (>90 L/h) [CL]	≈250–300 (≈15–18 L/h) [CL_R]
Metabolism	By conjugation to acylglucuronide (represents ≈11% of administered dose)	Not metabolized
Elimination	>97% in faeces via biliary excretion	Almost entirely as unchanged drug in urine

a Not clearly specified whether healthy volunteers or patients with hypertension.

b Some values reported in EU summary of product characteristics[18] differ from those reported in US prescribing information.[17]

c Over a dose range of 20–160 mg (not specified whether single- or multiple-dose regimens).

AUC = area under the plasma concentration-time curve; **CL** = total plasma clearance; **CL_R** = renal clearance; **C_{max}** = maximum plasma drug concentration; **F** = absolute bioavailability; **NR** = not reported; **$t_{½}$** = elimination half-life; **t_{max}** = time to reach C_{max}; **V_d** = apparent volume of distribution; ↑ indicates increase.

the pharmacokinetic properties of telmisartan may be related to its unique chemical properties. Telmisartan lacks the biphenyl tetrazole moiety that most of the commonly used ARBs possess and differs from the other non-tetrazole derivative, eprosartan, which has carboxylic acid groups at both ends of the molecule.[27]

2.2.1 Absorption and Distribution

Maximum plasma concentrations (C_{max}) of telmisartan are achieved 0.5–1.5 hours after oral administration.[18] In patients with hypertension who received telmisartan 40, 80 and 120 mg once daily for 4 weeks, mean C_{max} values were 130, 465 and 1046 ng/mL, respectively, and corresponding values for area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_∞) were 1304, 2651 and 4231 ng • h/mL.[28] The pharmacokinetics of telmisartan are non-linear over a dosage range of 20–160 mg, as greater than proportional increases in C_{max} and AUC values are observed with increasing doses.[18] Food reduces the bioavailability of telmisartan by ≈6% and ≈19%, respectively, with a 40 mg and 160 mg dose, although this is not expected to reduce the clinical efficacy of the drug.[18] Telmisartan is extensively bound to plasma proteins and its relatively high volume of distribution (table I) indicates additional tissue binding.

HCTZ has an absolute bioavailability of ≈60% and C_{max} values are achieved ≈1–3 hours after oral administration.[18] The bioavailability of HCTZ is dose-proportional when administered at clinically relevant dosages.[29,30] In a crossover study in healthy volunteers receiving single doses of HCTZ 12.5 and 25 mg (as well as higher doses not discussed here), mean C_{max} values were 70 and 142 ng/mL, and mean AUC_9 values were 351 and 613 ng • h/mL.[30] The volume of distribution of HCTZ is smaller than that for telmisartan and plasma protein binding is also less extensive (table I).

2.2.2 Metabolism and Elimination

After single-dose oral administration of ^{14}C-labelled telmisartan 40 mg in healthy volunteers, most of the total radioactivity in plasma represented the parent compound, although a small proportion (≈11%) represented its only metabolite, a pharmacologically inactive acylglucuronide.[31] At least 97% of an orally or intravenously administered dose was eliminated in the faeces by biliary excretion.[18,31] Importantly, telmisartan does not undergo metabolism via cytochrome P450 (CYP) isoenzymes and is, therefore, not likely to interact with substrates, inducers or inhibitors of CYP. Reported mean values for total clearance and $t_{½}$ of telmisartan vary somewhat,[17,18,24,28,31] and there is substantial inter-individual variation for these and other pharmacokinetic parameters of the drug.[24,28,31] EU summary of product characteristics states that the total plasma clear-

ance of telmisartan is >1500 mL/min (>90 L/h) and $t_{1/2}$ is >20 hours (table I).[18]

HCTZ does not undergo metabolism and is eliminated almost entirely as unchanged drug in the urine.[18] Elimination of HCTZ from plasma is biphasic, with the $t_{1/2}$ of the slower phase reported as 5.6–14.8 hours in healthy volunteers.[30] The EU summary of product characteristics reports a $t_{1/2}$ of 10–15 hours and renal clearance of ≈250–300 mL/min (≈15–18 L/h) for HCTZ (table I).[18]

2.2.3 Special Patient Populations

The pharmacokinetics of telmisartan were similar in elderly normotensive individuals (aged ≥65 years) and those aged <65 years,[28] and dosage adjustments are not necessary in elderly patients (section 5). Despite 2- to 3-fold higher plasma telmisartan concentrations in females than in males (including in elderly individuals[28]), dosage adjustments are not required because no significant differences were observed between men and women with respect to BP-lowering effects and the incidence of orthostatic hypotension in clinical trials.[18] Although a trend towards higher plasma HCTZ concentrations in females than in males was observed, the difference is not deemed to be clinically relevant.[18]

Because telmisartan is not eliminated renally, dosage adjustments are not necessary in patients with decreased renal function (section 5). However, HCTZ is almost exclusively eliminated via the kidneys (section 2.2.2) and, therefore, the $t_{1/2}$ of HCTZ increases and the renal clearance of the drug decreases with impaired renal function.[32] In a group of 23 individuals with varying degrees of renal function, mean $t_{1/2}$ values for HCTZ were 6.4, 11.5 and 20.7 hours in those with normal renal function, mild renal impairment (creatinine clearance [CL_{CR}] 30–90 mL/min) and severe impairment (CL_{CR} <30 mL/min).[32] No specific dosage adjustments are recommended for telmisartan/HCTZ in patients with mild to moderate impairment of renal function.[17,18] However, severe renal impairment (CL_{CR} <30 mL/min) is a contraindication in the EU summary of product characteristics[18] and US prescribing information states that telmisartan/HCTZ is not recommended in these patients[17] (section 5).

The bioavailability of telmisartan was increased in patients with hepatic impairment who received single doses of 20 or 120 mg in a crossover study.[33] Compared with healthy volunteers, patients with Child-Pugh scores of 6–9 had a 6.4-fold increase in C_{max} and a 2.7-fold increase in AUC_{∞} with the 20 mg dose. Following administration of telmisartan 120 mg, C_{max} and AUC_{∞} values were 3.2- and 3.1-fold higher in patients with hepatic impairment.[33] The EU summary of product characteristics[18] states that telmisartan/HCTZ is contraindicated in patients with severe hepatic impairment, cholestasis or biliary obstructive disorders. US prescribing information[17] states that telmisartan/HCTZ is not recommended for patients with severe hepatic impairment and advises that the fixed-dose combination be used with caution in patients with biliary obstructive disorders or hepatic insufficiency (section 5).

2.2.4 Drug Interactions

Because telmisartan is not metabolized by CYP isoenzymes and HCTZ is eliminated renally (section 2.2.2), there is little potential for interactions between telmisartan/HCTZ and substrates, inducers or inhibitors of CYP isoenzymes.[17,18] The possible exception is that telmisartan may inhibit the metabolism of drugs that are substrates for CYP2C19 because telmisartan exhibited some inhibition of this CYP isoenzyme *in vitro*.[17] Both telmisartan and HCTZ are associated with drug interactions of potential clinical significance,[17,18] and local prescribing information should be consulted. Most of these drug interactions are pharmacodynamic in nature. For example, thiazide diuretics can reduce serum potassium levels (although this can be offset by ARBs such as telmisartan), impair glucose tolerance and increase serum uric acid levels, and may, therefore, interact with drugs that induce potassium loss or are affected by serum potassium disturbances, or are used in the treatment of diabetes or gout. However, some pharmacokinetic interactions may also occur. Most notably, diuretics reduce the renal clearance of lithium thereby increasing the risk of lithium

toxicity; such combinations are generally not recommended.[17,18] In addition, concomitant administration of telmisartan and digoxin was associated with 49% and 20% increases in peak and trough plasma digoxin concentrations, respectively, and monitoring of digoxin concentrations is recommended when initiating, adjusting or discontinuing telmisartan therapy.[17]

No drug interaction studies have been conducted with fixed-dose combinations of telmisartan/HCTZ and other drugs, although rare cases of reversible increases in serum lithium concentrations and toxicity have been reported with concurrent use of telmisartan/HCTZ and lithium,[18] and coadministration of these drugs is not recommended.[17,18]

3. Therapeutic Efficacy

A number of well designed clinical trials have evaluated the BP-lowering efficacy of telmisartan/HCTZ in adult patients (aged ≥18 years) with hypertension. These include large, randomized comparisons between telmisartan/HCTZ and telmisartan monotherapy (section 3.1), other ARBs plus HCTZ (section 3.2) and antihypertensive agents from other drug classes (ACE inhibitors or calcium channel antagonists) with or without HCTZ (section 3.3). Various subgroup analyses and long-term extension studies are available, and these data are presented in the appropriate subsections. In addition, results of phase IV community-based studies are presented in section 3.1.1 and section 3.1.2, and those from a large randomized trial comparing low- and high-dose regimens of telmisartan/HCTZ are discussed in section 3.4. All of the trials are fully published, with the exception of studies reported in section 3.1.2 and section 3.4, which are available as abstracts. All antihypertensive agents evaluated in the clinical trials were administered orally.

3.1 Comparisons with Telmisartan Monotherapy

The comparative efficacy of telmisartan/HCTZ and telmisartan monotherapy has been evaluated in three large, randomized, double-blind, multicentre trials in patients with mild to moderate hypertension, defined as trough seated[34,35] or supine[36] DBP 95–114 mmHg and SBP 140–200 mmHg (table II). In two of the trials, randomization occurred after an inadequate response (DBP ≥90 mmHg) to 4[35] or 8[34] weeks of telmisartan monotherapy. In the third trial, which used a 4×5 factorial design, randomization occurred after a 4-week single-blind placebo run-in phase.[36] The double-blind treatment phase was 8 weeks in all three trials, with the primary endpoint being reduction from baseline in mean trough seated[34,35] or supine[36] DBP. In the two trials by Lacourcière et al.,[34,35] a difference between treatment groups of ≥3 mmHg for reduction in mean trough DBP was deemed to be clinically significant.

Baseline characteristics of patients in all three trials were similar other than for race.[34-36] The factorial trial had a target of 30% Black patients, and 27% of patients included in the efficacy analysis were Black,[36] whereas ≥95% of patients in the other two trials were Caucasian.[34,35] Across the three studies, mean age ranged from ≈53 to 55 years and ≈60% of patients were male. The mean or median duration of hypertension was broadly similar (≈6–9 years), as were baseline BP values. The overall mean baseline SBP/DBP in the factorial trial was 154.0/100.7 mmHg[36] and baseline BP values for the specific groups in the other trials are presented in table II. There were no important between-group differences in baseline characteristics in any of the trials.[34-36]

The main findings, including the primary efficacy outcomes for the intent-to-treat (ITT) populations, are presented in table II. In the two trials by Lacourcière et al.,[34,35] patients whose BP did not respond to monotherapy with telmisartan 40 mg[35] or 80 mg[34] once daily were randomized to receive either the corresponding fixed-dose combination of telmisartan/HCTZ (40 mg/12.5 mg[35] or 80 mg/12.5 mg[34]) once daily or to continue telmisartan monotherapy for 8 weeks. Results showed that fixed-dose combinations of telmisartan/HCTZ provided statistically and clinically significant additional BP-lowering efficacy compared with telmisartan monotherapy in nonresponders to telmisartan mono-

Table II. Comparative efficacy of combinations of telmisartan plus hydrochlorothiazide (TEL/HCTZ) and TEL monotherapy. Summary of randomized, double-blind, multicentre trials comparing TEL/HCTZ with TEL monotherapy in patients (pts) with mild to moderate hypertension (trough seated[34,35] or supine[36] diastolic blood pressure (DBP) 95–114 mmHg and systolic blood pressure (SBP) 140–200 mmHg). Randomization to study treatment occurred after a 4-wk placebo (PL) run-in period[36] or after an inadequate response to 4 or 8 wk of TEL monotherapy.[34,35] All agents were administered orally once daily for 8 wk, and results of the intent-to-treat (ITT) analysis are presented

Study	Dosage (mg/day)	No. of pts	Mean trough seated[34,35] or supine[36] SBP/DBP[a] (mmHg)		Responders (%)[b]
			baseline	reduction at endpoint	
Lacourcière et al.[34]	TEL/HCTZ 80/12.5	246	148.9/96.4	12.6**/8.0**	41.5*[c]
	TEL 80	245	148.7/96.6	7.0/4.9	26.1[c]
Lacourcière and Martin[35]	TEL/HCTZ 40/12.5	159	147.1/95.7	10.8**[d]/7.4**	51.6*
	TEL 40	162	146.7/95.6	3.4[d]/3.9	23.5
McGill and Reilly[36] [e]	TEL/HCTZ 80/12.5	73	NR[f]	23.9**†/14.9**†	79
	TEL/HCTZ 40/12.5	70	NR[f]	18.8**/12.6	63
	TEL 80	77	NR[f]	15.4‡‡/11.5‡‡	69
	TEL 40	75	NR[f]	12.2‡‡/10.7‡‡	67
	HCTZ 12.5	73	NR[f]	6.9‡/7.3‡‡	47
	PL	73	153.7/100.3	2.9/3.8	29

a Primary endpoint was the reduction in mean seated[34,35] or supine[36] DBP from baseline.

b Pts with trough seated SBP/DBP <140/90 mmHg[34,35] or supine DBP ≤90 mmHg and/or a ≥10 mmHg reduction from baseline.[36]

c Responder rate evaluated in 235 pts in TEL/HCTZ group and 230 pts in the TEL monotherapy group who completed all three scheduled clinic visits during the 8-wk double-blind phase.

d SBP reductions estimated from a graph.

e The study used a 4 × 5 factorial design (HCTZ 0, 6.25, 12.5, 25 mg; TEL 0, 20, 40, 80, 160 mg) and had a total of 807 pts in the ITT population; results are not presented for all dosage regimens.

f Baseline SBP/DBP was 154.0/100.7 mmHg across all treatment groups.

NR = not reported; * $p < 0.05$, ** $p < 0.01$ vs TEL and/or HCTZ monotherapy; † $p < 0.05$ vs TEL/HCTZ 40/12.5; ‡ $p < 0.05$ vs PL, ‡‡ $p < 0.01$ vs PL.

therapy.[34,35] Both trials showed significantly greater reductions in mean trough seated DBP (primary endpoint) and SBP (both $p < 0.01$), as well as significantly greater response rates ($p < 0.05$), with telmisartan/HCTZ fixed-dose regimens compared with the same dosage of telmisartan as monotherapy. Response was defined as mean trough seated SBP/DBP <140/90 mmHg in both studies.

The key results of the factorial trial are also presented in table II and show that once-daily telmisartan/HCTZ had significantly greater BP-lowering efficacy than either component used as monotherapy at the same dosage.[36] In particular, telmisartan/HCTZ 80 mg/12.5 mg was associated with significantly greater reductions in both mean trough supine DBP (primary endpoint) and SBP (both $p < 0.01$) than either telmisartan 80 mg or HCTZ 12.5 mg. Telmisartan/HCTZ 80 mg/12.5 mg also achieved significantly ($p < 0.05$) greater reductions in SBP/DBP than telmisartan/HCTZ 40 mg/12.5 mg. The reduction from baseline in SBP, but not in DBP, with telmisartan/HCTZ 40 mg/12.5 mg was significantly greater than that with telmisartan 40 mg or HCTZ 12.5 mg monotherapy. Unlike the trials by Lacourcière et al.,[34,35] the factorial trial used a placebo run-in phase prior to randomization and, therefore, did not focus on nonresponders to telmisartan monotherapy.[36]

Results of a subgroup analysis using data from the 219 Black participants in the factorial trial (27% of the ITT population)[37] were generally similar to those for the overall study population.[36] After 8 weeks of once-daily therapy, mean reductions from baseline in trough supine SBP/DBP were 21.5/13.3 mmHg with telmisartan/HCTZ 80 mg/12.5 mg and 14.3/10.0 mmHg with telmisartan/HCTZ 40 mg/12.5 mg compared with 7.8/4.6 mmHg with telmisartan 80 mg, 2.0/6.7 mmHg with telmisartan 40 mg and 9.2/5.2 mmHg with HCTZ 12.5 mg.[37] Reductions from baseline in both DBP (primary

endpoint) and SBP were significantly greater with telmisartan/HCTZ 80 mg/12.5 mg than telmisartan 80 mg or HCTZ 12.5 mg ($p < 0.01$ for all comparisons). Telmisartan/HCTZ 40 mg/12.5 mg achieved statistically significant reductions in SBP relative to telmisartan 40 mg ($p \leq 0.01$) and in DBP versus HCTZ 12.5 mg ($p = 0.05$).

In open-label, multicentre, 1-year (n = 483)[38] and 4-year (n = 888)[39] extensions of trials evaluating telmisartan monotherapy in patients with mild to moderate hypertension, HCTZ 12.5 or 25 mg once daily was added to telmisartan 40 or 80 mg once daily, if necessary, to achieve control of DBP (<90 mmHg). Results showed that telmisartan/HCTZ achieved and maintained clinically relevant reductions in BP over the long term in patients with mild to moderate hypertension.[38,39] For example, at the end of the 4-year extension study (an open-label follow-up study of four controlled trials with telmisartan not discussed in this section), 65% of patients were receiving telmisartan monotherapy, 23% were treated with telmisartan/HCTZ, and 12% received telmisartan plus another antihypertensive with or without HCTZ.[39] Overall, 84% of patients achieved control of DBP, including 79% of those who received telmisartan/HCTZ.

3.1.1 Phase IV MICCAT2 Trial in Community Practice

Although not specifically designed to compare telmisartan/HCTZ with monotherapy, results of MICCAT2 (Micardis Community Ambulatory Monitoring Trial), a phase IV study conducted in the community practice setting, are also relevant.[40] Various reports are available from the community-based, open-label study in patients with stage I or II hypertension (office DBP ≥90 and ≤109 mmHg or office SBP ≥140 and ≤179 mmHg) who were not receiving any antihypertensive therapy or who were treated with only a single antihypertensive agent or a two-drug fixed-dose combination (typically including a diuretic).[40-42] At baseline, 24-hour ambulatory blood pressure monitoring (ABPM) was performed and any previous antihypertensive therapy was then discontinued. Patients were immediately started on telmisartan 40 mg once daily for 2 weeks, followed by 4 weeks of telmisartan 80 mg once daily and a further 4 weeks of the same therapy if office BP goal was achieved. Patients whose office BP was not <140/90 mmHg (i.e. Joint National Committee [JNC]-7 goal) received telmisartan/HCTZ 80 mg/12.5 mg once daily for the last 4 weeks of the study. At the end of the study period (either on monotherapy or combination therapy), 24-hour ABPM was performed again.

The main analysis was conducted in 1469 patients, including 1296 Caucasian and 173 Black patients.[40] A greater proportion of Black than Caucasian patients required combination therapy (52.6% vs 40.6%; $p = 0.0047$), but BP-reductions, as measured by ABPM, were similar in Caucasian and Black patients. Moreover, when patients with baseline ABPM <130/80 mmHg were excluded (to eliminate those with 'white-coat hypertension' [28% of patients]), changes in BP, as measured by ABPM, were similar between Caucasian and Black patients. Again, a higher proportion of Black than Caucasian patients required combined therapy (52.1% vs 39.5%; $p = 0.04$). Among previously untreated patients, office BP goal was attained in 80.8% of Caucasians and 74.0% of Blacks (not statistically significant), and ABPM goal (<130/80 mmHg) was achieved in 63.2% versus 48.0% ($p < 0.05$). Results indicate that combining HCTZ with telmisartan provides additional BP-lowering efficacy to achieve JNC-7 and ABPM-based BP goals in both Black and Caucasian patients in a community practice setting.

3.1.2 Phase IV SURGE-2 Trial in Community Practice

The SURGE-2 (Study of hypertensive population Under treatment with telmisartan in Real clinical conditions with the Goal to control the Early morning BP rise) trial was a practice-based study similar to MICCAT2 (section 3.1.1) that used home BP monitoring to evaluate the antihypertensive efficacy of once-daily telmisartan 80 mg with or without HCTZ 12.5 mg for 8 weeks in a large cohort of patients (n = 8193) with previously treated or untreated hypertension (office BP >140/90 mmHg).[43,44] Treatment could be adjusted if office BP remained ≥140/90 mmHg. Mean morning

home BP was significantly reduced from baseline by 22/12 mmHg with telmisartan alone or in combination with HCTZ (p-value not stated).[43] Reductions from baseline in average home BP (morning, noon and evening measurements) were 20/10 mmHg. Using the JNC-7 threshold for hypertension, 45% of patients achieved a morning home BP value <135/85 mmHg.[43]

In addition, ABPM was performed at baseline and at the end of the 8-week study period in 863 patients.[44] Telmisartan with or without HCTZ significantly reduced mean morning ambulatory BP by 8.2/4.9 mmHg ($p < 0.001$) and 24-hour ambulatory BP by 7.7/4.7 mmHg ($p < 0.001$) from baseline. A total of 64.4% of patients achieved the target morning ambulatory BP of <135/85 mmHg after 8 weeks of treatment compared with 36.5% of patients at baseline.[44]

Together, results of these analyses (both of which are available as abstracts) show that once-daily telmisartan with or without HCTZ provides satisfactory control of BP in the morning hours and throughout the dose administration interval in a 'real world' setting.[43,44]

3.2 Comparisons with Other Angiotensin II Receptor Blockers Plus Hydrochlorothiazide (HCTZ)

Several randomized trials have compared the antihypertensive efficacy of telmisartan/HCTZ with that of other ARBs plus HCTZ, as discussed in the following subsections. Two large noninferiority studies comparing telmisartan/HCTZ with valsartan/HCTZ used clinic BP measurements to assess efficacy,[45,46] whereas all other comparisons between telmisartan/HCTZ and ARBs plus HCTZ focused on ABPM.

3.2.1 Versus Valsartan/HCTZ

Two large noninferiority trials compared the BP-lowering efficacy of telmisartan/HCTZ 80 mg/25 mg and valsartan/HCTZ 160 mg/25 mg once daily for 8 weeks in patients with stage 1 or 2 hypertension.[45,46] Both the original study (n = 1066)[45] and the subsequent confirmatory trial (n = 1181)[46] were randomized, double-blind, placebo-controlled, multicentre studies that included a 1-week washout period (for patients who were receiving antihypertensive therapy) followed by a 2- to 3-week single-blind period. Patients whose trough seated DBP remained ≥95 mmHg (but <120 mmHg) were randomized to receive 2 weeks of treatment with once-daily telmisartan 80 mg, valsartan 160 mg or placebo followed by 6 weeks of treatment with once-daily telmisartan/HCTZ 80 mg/25 mg, valsartan/HCTZ 160 mg/25 mg or placebo for the respective treatment groups. The primary efficacy endpoints were the change from baseline in trough seated DBP and SBP. Both trials used a hierarchal model to analyse results; if noninferiority of telmisartan/HCTZ to valsartan/HCTZ was proven, confirmatory testing was planned to establish whether telmisartan/HCTZ was superior to valsartan/HCTZ.

Baseline characteristics were similar between trials and across treatment groups within each trial.[45,46] In both trials, mean age was ≈53 years, mean baseline BP was 155/102 mm/Hg, about one-quarter of patients were Black and there was a greater proportion of male than female patients.

An overview of results of the two studies is presented in figure 1. Compared with placebo, both active treatments produced marked reductions in BP. After adjustment for gender and race with both baseline response and age as co-variates, telmisartan/HCTZ 80 mg/25 mg once daily was associated with significantly greater reductions in both DBP (mean difference −1.8 mmHg; 95% CI −3.0, −0.6; $p = 0.019$) and SBP (mean difference −2.8 mmHg; 95% CI −4.6, −1.0; $p = 0.0039$) than valsartan/HCTZ 160 mg/25 mg once daily in the original study (n = 1066 evaluable patients).[45] These results were confirmed in the follow-up trial, showing adjusted mean differences of −1.2 mmHg (95% CI −2.3, −0.2; $p = 0.0254$) for DBP and −2.1 mmHg (95% CI −3.9, −0.4) for SBP, both favouring telmisartan/HCTZ over valsartan/HCTZ (n = 1115 evaluable patients).[46]

Fixed-dose combinations of telmisartan/HCTZ 80 mg/12.5 mg and valsartan/HCTZ 160 mg/12.5 mg once daily were compared for their effects

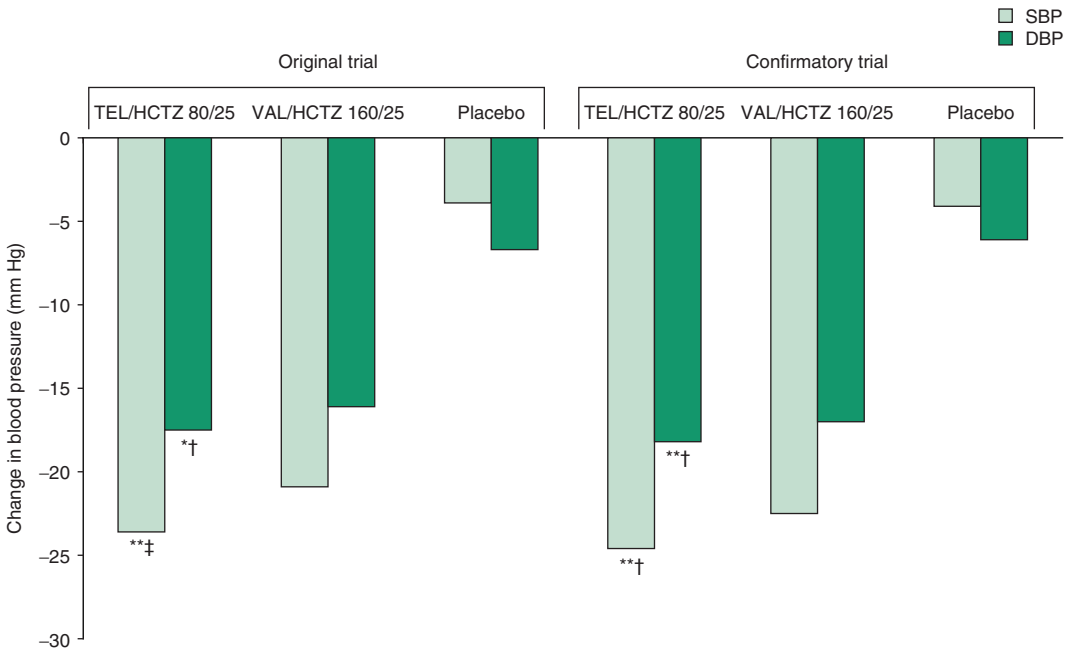

Fig. 1. Results of two randomized, double-blind, placebo-controlled trials comparing fixed-dose combinations of telmisartan plus hydrochlorothiazide (TEL/HCTZ) and valsartan plus HCTZ (VAL/HCTZ). Patients with stage 1 or 2 hypertension (trough seated diastolic blood pressure [DBP] ≥95 mmHg but <120 mmHg after placebo run-in phase) received TEL/HCTZ 80 mg/25 mg or VAL/HCTZ 160 mg/25 mg orally once daily for 8 wk in both the original trial (n = 1066)[45] and the confirmatory trial (n = 1115).[46] Data shown are changes from baseline in mean trough seated systolic (SBP) and DBP (primary endpoints). Reductions in blood pressure were adjusted for gender and race with both baseline response and age as co-variates. If noninferiority of TEL/HCTZ to VAL/HCTZ was proven, confirmatory testing was planned to establish whether TEL/HCTZ was superior to VAL/HCTZ. Statistical analysis (p-values) not reported for VAL/HCTZ vs placebo. * $p < 0.01$, ** $p < 0.0001$ vs placebo; † $p < 0.05$, ‡ $p < 0.01$ vs VAL/HCTZ.

on early morning BP (primary endpoint) and various secondary endpoints, as assessed by ABPM, in 840 obese hypertensive patients with type 2 diabetes in the SMOOTH (Study of Micardis [telmisartan] in overweight/obese patients with type 2 diabetes and hypertension) trial.[47] Results of the 10-week, randomized, open-label (blinded-endpoint), multicentre trial showed significant differences favouring telmisartan/HCTZ for reductions in SBP (difference 3.9 mmHg; $p < 0.0001$) and DBP (2.0 mmHg; $p = 0.0007$) during that last 6 hours of the dose administration interval. Telmisartan/HCTZ also provided greater reductions in mean 24-hour, morning, daytime and night-time ambulatory BP than valsartan/HCTZ. Mean reductions in trough seated clinic SBP (difference 3.2 mmHg; $p = 0.0017$) and DBP (difference 1.2 mmHg; $p = 0.0446$) were also significantly greater with telmisartan/HCTZ than valsartan/HCTZ.

3.2.2 Versus Losartan/HCTZ

Reduction in ambulatory DBP during the last 6 hours of the dose administration interval was the primary endpoint in two randomized, open-label (blinded-endpoint), multicentre trials[48,49] comparing telmisartan/HCTZ 40 mg/12.5 mg and 80 mg/12.5 mg once daily versus losartan/HCTZ 50 mg/12.5 mg once daily for 6 weeks in patients with mild to moderate hypertension (mean seated DBP 90–109 mmHg and [after 2- to 4-week placebo run-in period] 24-hour mean DBP ≥85 mmHg). A pooled analysis of these two similarly designed trials included 1402 patients (62% male) with a mean age of 53 years.[50]

Results of the pooled analysis showed statistically significant advantages in terms of early morning

DBP reductions for both regimens of telmisartan/HCTZ over losartan/HCTZ.[50] Mean reductions in ambulatory DBP during the last 6 hours of the once-daily dose administration interval were 11.3, 12.0 and 9.4 mmHg for telmisartan/HCTZ 40 mg/12.5 mg, telmisartan/HCTZ 80 mg/12.5 mg and losartan/HCTZ 50 mg/12.5 mg, respectively, after adjustment for baseline and study effects, and for possible treatment-by-study interaction ($p < 0.001$ for both comparisons between telmisartan/HCTZ and losartan/HCTZ). Assessment of secondary outcomes showed that mean reductions in last-6-hour ambulatory SBP (after adjustment) were 17.2, 18.0 and 14.6 mmHg in the respective treatment groups ($p < 0.001$ for both comparisons between telmisartan/HCTZ and losartan/HCTZ). In addition, there were statistically significant advantages ($p < 0.01$ or $p < 0.001$) for both telmisartan/HCTZ regimens over losartan/HCTZ in terms of adjusted mean reductions in 24-hour ambulatory SBP and DBP, as well as for mean reductions in trough seated (clinic) SBP and DBP. In general, the magnitude of these differences was broadly similar to that observed in early morning ABPM.

3.2.3 Versus Olmesartan/HCTZ

A significantly greater antihypertensive effect was observed with telmisartan/HCTZ 80 mg/12.5 mg than olmesartan/HCTZ 20 mg/12.5 mg in a randomized study in patients with hypertension (DBP ≥99 mmHg and <110 mmHg) [figure 2].[51] After a 2-week washout period, 126 patients were randomized to receive telmisartan 80 mg or olmesartan 20 mg once daily as monotherapy for 8 weeks, after which HCTZ 12.5 mg once daily was added for a further 8 weeks in patients whose BP was not controlled (DBP ≥90 mmHg) with monotherapy. Mean reductions from baseline in ABPM values (SBP/DBP) were significantly ($p < 0.05$) greater with telmisartan/HCTZ ($n = 49$) than olmesartan/HCTZ ($n = 52$) for 24-hour (21.5/14.6 vs 18.8/12.3 mmHg), daytime (21.8/14.9 vs 19.3/12.8 mmHg) and night-time (20.4/13.7 vs 17.4/10.6 mmHg) measurements. The greatest difference between groups was observed during night-time ABPM.

3.3 Comparisons with ACE Inhibitor or Calcium Channel Antagonists With or Without HCTZ

Three studies used ABPM to compare the BP-lowering efficacy of telmisartan/HCTZ with that of antihypertensives other than ARBs (lisinopril/HCTZ,[23] nifedipine GITS[22] and amlodipine/HCTZ[52]). Pharmacodynamic data (changes in sympathetic activation and cognitive function) from two of the studies[22,23] are presented in section 2.1.

In a 24-week, randomized, open-label (blinded endpoint) trial, 160 elderly (aged 61–75 years) patients with hypertension (seated DBP ≥95 and <110 mmHg, and SBP >140 mmHg) received, after an initial 2-week washout period, 24 weeks of treatment with telmisartan/HCTZ 80 mg/12.5 mg or lisinopril/HCTZ 20 mg/12.5 mg once daily.[23] Both treatments significantly ($p < 0.01$) decreased ambulatory SBP and DBP compared with baseline; however, adjusted mean differences between groups for reductions from baseline in ambulatory SBP and DBP were significantly greater with telmisartan/HCTZ than lisinopril/HCTZ for 24-hour (ΔSBP 2.41 mmHg, ΔDBP 1.94 mmHg; both $p < 0.05$), daytime (ΔSBP 2.37 mmHg, ΔDBP 1.73 mmHg; both $p < 0.05$) and night-time (ΔSBP 2.46 mmHg, $p < 0.05$; ΔDBP 2.48, $p < 0.01$) measurements. Trough to peak ratios (ratio between antihypertensive effect and the end of the dose administration interval to that at the maximum effect) and smoothness index (mean of 24-hour ambulatory BP change divided by the corresponding standard deviation) values for SBP and DBP were similar for the two antihypertensive regimens, indicating a relatively consistent antihypertensive effect over the entire once-daily dose administration interval.[23]

Telmisartan/HCTZ 80 mg/12.5 mg once daily ($n = 62$) was compared with nifedipine GITS 60 mg once daily ($n = 62$) for 12 weeks in a randomized, open-label (blinded-endpoint) study.[22] Patients with seated DBP ≥95 and <110 mmHg after a 2-week washout period were included in the trial, and ABPM was conducted at the end of the 12-week active treatment period. Both treatments significantly ($p < 0.001$) decreased ambulatory SBP and DBP

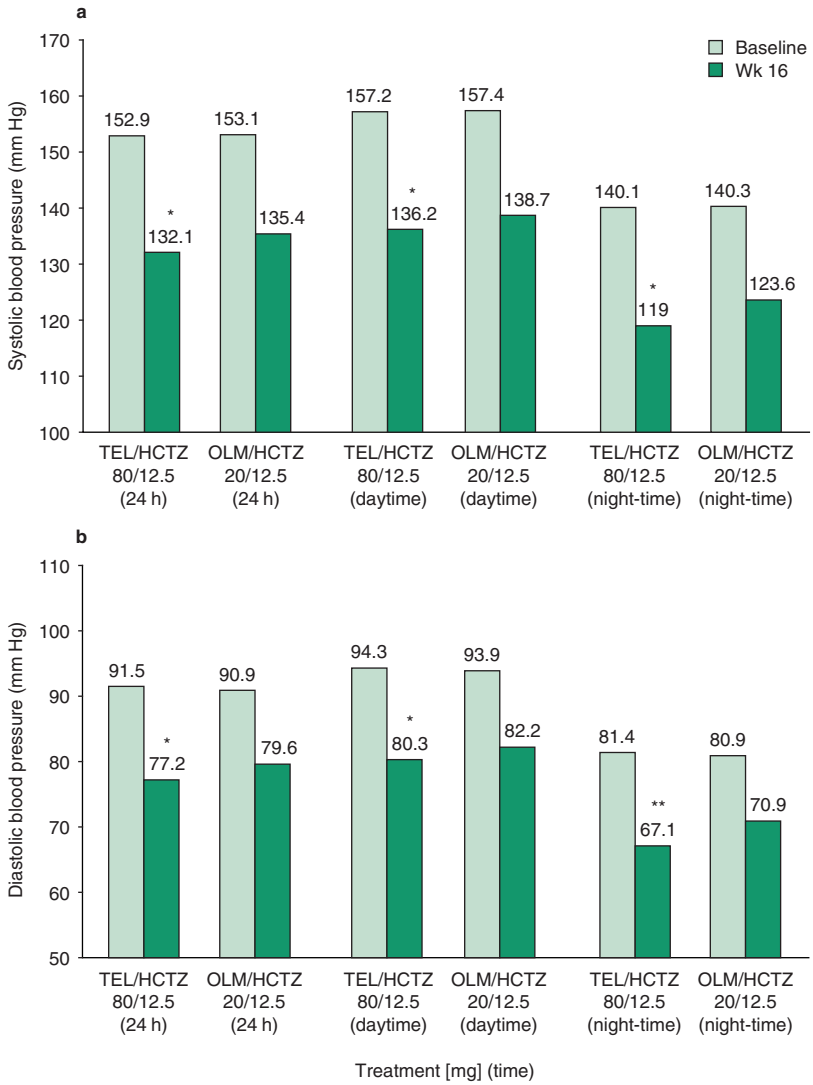

Fig. 2. Mean changes in ambulatory blood pressure with telmisartan (TEL) or olmesartan (OLM) in combination with hydrochlorothiazide (HCTZ) in patients with moderate hypertension.[51] A total of 126 patients were randomized to receive TEL 80 mg or OLM 20 mg once daily for 8 wk, after which HCTZ 12.5 mg once daily was added for a further 8 wk in those patients whose diastolic blood pressure remained ≥90 mmHg (n = 101). Ambulatory blood pressure changes from baseline to wk 16 are presented for (**a**) systolic blood pressure and (**b**) diastolic blood pressure. * $p < 0.05$, ** $p < 0.01$ for TEL/HCTZ vs OLM/HCTZ.

compared with baseline; however, adjusted mean differences between groups for reductions from baseline in ambulatory SBP and DBP were significantly greater with telmisartan/HCTZ than nifedipine GITS for 24-hour ($p < 0.001$ for SBP and DBP), daytime ($p < 0.001$ for SBP and DBP) and night-time ($p < 0.01$ for SBP and $p < 0.05$ for DBP) measurements. Trough to peak ratios for SBP and DBP were similar for the two antihypertensive regimens, although smoothness index significantly ($p < 0.05$) favoured telmisartan/HCTZ for both SBP and DBP.[22]

In another trial, telmisartan/HCTZ 80 mg/12.5 mg once daily was compared with amlodipine/

HCTZ 10 mg/12.5 mg once daily in older patients (aged ≥60 years) with predominantly systolic hypertension (SBP 141–179 mmHg, DBP ≤95 mmHg and, at the end of a 2- to 4-week placebo run-in period, mean ambulatory SBP >125 mmHg).[52] The randomized, open-label (blinded-endpoint), multicentre trial included a 14-week active treatment period during which randomized patients initially received once-daily telmisartan 40 mg or amlodipine 5 mg for 2 weeks, followed by forced titration to telmisartan 80 mg or amlodipine 10 mg for 6 weeks, with the addition of HCTZ 12.5mg once daily for all patients at week 8. The primary endpoint was the reduction from baseline in mean ambulatory SBP during the last 6 hours of the dose administration interval at the end of the 14-week treatment period, with the primary analysis testing for noninferiority of telmisartan/HCTZ versus amlodipine/HCTZ. Noninferiority was shown if the upper limit of the 95% CI of the adjusted mean difference for the primary endpoint was <3 mmHg. A total of 1000 patients were randomized, although most analyses were conducted on the full analysis set of 872 patients. The majority of patients were Caucasian (99%), female (58%) and had been receiving antihypertensive therapy (62%).

Results of the study showed that telmisartan/HCTZ was noninferior to amlodipine/HCTZ with respect to the primary endpoint.[52] The adjusted mean changes in last-6-hour ambulatory SBP for the respective groups were −18.3 and −17.4 mmHg; the resulting difference was −0.8 mmHg and 95% CI values were −2.2 and 0.6 (i.e. the upper limit of the 95% CI was <3 mmHg). The superiority of telmisartan/HCTZ over amlodipine/HCTZ for the primary endpoint (a hierarchal procedure specified in the protocol if noninferiority was demonstrated) could not be shown (p = 0.2520). However, reductions in mean ambulatory SBP were significantly ($p \leq 0.05$) greater with telmisartan/HCTZ than amlodipine/HCTZ for 24-hour, daytime and morning (but not night-time) measurements. The proportion of patients who achieved control of SBP (24-hour mean ambulatory SBP <130 mmHg at week 14) was also significantly higher with telmisartan/HCTZ than amlodipine/HCTZ (65.9% vs 58.3%; p = 0.0175).

3.4 Comparison of Telmisartan/HCTZ 80 mg/12.5 mg versus 80 mg/25 mg

The use of telmisartan/HCTZ 80 mg/25 mg once daily in hypertensive patients not responsive to telmisartan/HCTZ 80 mg/12.5 mg once daily was shown to be an effective treatment strategy in a randomized, double-blind trial (reported as an abstract).[53] Patients (mainly Caucasians) with DBP ≥95 mmHg (if current antihypertensive therapy included one drug) or ≥90 mmHg (if receiving two or three drugs) were enrolled and underwent a 6-week run-in period with telmisartan/HCTZ 80 mg/12.5 mg once daily. Patients whose trough seated DBP was ≥90 mmHg after the run-in period were randomized (n = 713) to continue with the lower-dose regimen or to receive the higher-dose regimen for 8 weeks. Reduction from baseline in trough seated DBP was the primary endpoint. Baseline mean trough seated DBP values were 95.0 and 95.3 mmHg in the lower- and higher-dose groups.

Results of the trial showed adjusted mean changes from baseline in trough seated DBP were −5.5 and −7.1 mmHg in the lower- and higher-dose groups, and the difference between treatment groups (−1.6 mmHg; 95% CI −2.5, −0.6) was statistically significant (p = 0.001).[53] Corresponding results for adjusted mean changes from baseline in trough seated SBP were −7.1 and −9.8 mmHg, with the between-group difference (−2.7 mmHg; 95% CI −4.2, −1.2) significantly ($p < 0.001$) favouring the higher-dose regimen of telmisartan/HCTZ. In addition, more patients treated with telmisartan/HCTZ 80 mg/25 mg than 80 mg/12.5 mg once daily achieved a trough seated DBP <90 mmHg or a reduction from baseline of ≥10 mmHg (59.7% vs 51.9%; p = 0.034).

Data from a long-term extension of the trial (also reported as an abstract), in which 639 patients who completed the double-blind study received telmisartan/HCTZ 80 mg/25 mg once daily for 24 weeks, showed that 71.4% of patients achieved a trough seated DBP <90 mmHg (primary endpoint) at week 24 compared with 52.4% of patients at baseline (i.e.

entry into the extended phase).[54] Approximately 17% of patients (n = 111) required additional antihypertensive medication. In this subgroup of patients, DBP control increased from 24.8% at baseline to 58.6% at the end of the 24-week extension period. Reductions from baseline to week 24 in SBP/DBP were 4.1/3.1 mmHg in patients treated with telmisartan/HCTZ only and 7.3/5.5 mmHg in those who also received additional antihypertensive treatment.

4. Tolerability

Tolerability data on the combined use of telmisartan/HCTZ presented in this section are derived primarily from EU summary of product characteristics[18] and US prescribing information,[17] as well as larger comparative trials between telmisartan/HCTZ and telmisartan monotherapy (section 3.1)[34-36] or other antihypertensive agents (section 3.2[45,46,50] and section 3.3[22,23,52]). Additional data are available from a retrospective analysis of clinical trials with telmisartan with or without HCTZ.[55]

In clinical trials with telmisartan/HCTZ, in which >1700 patients received the combination (including 420 who received treatment for >1 year), no unexpected adverse events were reported that had not been previously reported with the individual drugs.[17] Overall, the incidence of adverse events with telmisartan/HCTZ was similar to that with placebo[17] or telmisartan monotherapy,[17,18] and most adverse events were mild, transient and did not necessitate discontinuation of therapy.[17]

According to the EU summary of product characteristics, specific adverse events have occurred more frequently with telmisartan/HCTZ than with placebo in clinical trials.[18] Among those adverse events deemed to be common (incidence >1% but <10%) and reported significantly ($p \leq 0.05$) more frequently with telmisartan/HCTZ than with placebo are infections (e.g. bronchitis, pharyngitis, sinusitis, upper respiratory tract infection), hypercholesterolaemia, hypokalaemia, anxiety, dizziness, vertigo, gastrointestinal disorders (e.g. abdominal pain, diarrhoea), eczema, musculoskeletal and connective tissue disorders (e.g. arthralgia), erectile dysfunction,

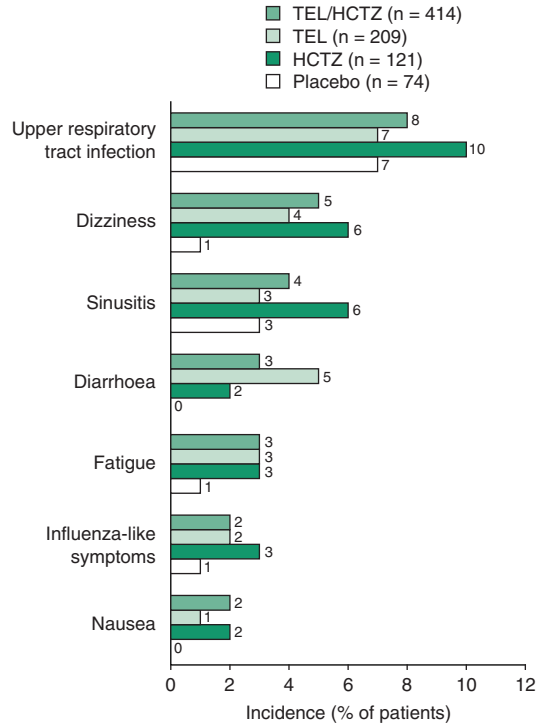

Fig. 3. Adverse events reported in ≥2% of patients treated with telmisartan/hydrochlorothiazide (TEL/HCTZ) in clinical trials (data from US prescribing information).[17] Patients with hypertension received TEL 20–160 mg/day, HCTZ 6.25–25 mg/day or combinations of TEL/HCTZ at these dosages. Statistical analysis was not reported.

influenza-like illness and pain. In addition, hypersensitivity, inadequate control of diabetes and hyperuricaemia were deemed to be uncommon (incidence >0.1% but <1%) and occurred significantly ($p \leq 0.05$) more frequently with telmisartan/HCTZ than with placebo. Dosages of telmisartan/HCTZ were not specified, but data are from all clinical trials.[18]

US prescribing information provides data on adverse events that were reported in ≥2% of patients treated with telmisartan/HCTZ and occurred with greater frequency than in placebo recipients, although statistical analysis was not reported.[17] These data are presented in figure 3 and reflect the use of all dosages of telmisartan (20–160 mg/day) plus HCTZ (6.25–25 mg/day). In addition, the following adverse events were reported more frequent-

ly with telmisartan/HCTZ than with placebo (statistical analysis not provided), but with an incidence <2% among recipients of telmisartan/HCTZ: back pain, dyspepsia, vomiting, tachycardia, hypokalaemia, bronchitis, pharyngitis, rash, postural hypotension and abdominal pain. As mentioned in section 2.1, coadministration of an ARB tends to reverse the potassium loss associated with thiazide diuretics.

Tolerability data for telmisartan/HCTZ reported in EU summary of product characteristics and US prescribing information are generally supported by those from a retrospective analysis of 50 phase IIIb/IV, double-blind (n = 8023) or open-label (n = 8393) studies with telmisartan 10–160 mg alone or in combination with HCTZ 6.25–25 mg once daily in patients with hypertension.[55] Planned treatment duration ranged from 1 week to 2 years and the majority of telmisartan-treated patients received once-daily telmisartan 40–80 mg with or without HCTZ 12.5–25 mg. In the double-blind and open-label studies, 1843 and 2486 patients, respectively, received combination therapy with telmisartan/HCTZ. Overall, the tolerability profile of telmisartan/HCTZ, telmisartan alone and placebo were deemed to be broadly similar, with the most frequent adverse events being dizziness and headache. Discontinuation of treatment because of an adverse event occurred in 4.7% of patients receiving telmisartan/HCTZ and 4.5% of those treated with telmisartan monotherapy compared with 4.6% of placebo recipients.[55] There appears to be no relationship between adverse events with telmisartan/HCTZ and age, gender or race.[17,18,55]

Large clinical trials comparing telmisartan/HCTZ with telmisartan monotherapy (section 3.1) showed a similar incidence of adverse events between treatment groups, and adverse events were typically mild and transient, with the majority of events deemed unrelated to treatment.[34-36] In double-blind comparisons of telmisartan/HCTZ 40 mg/12.5 mg[35] or 80 mg/12.5 mg[34] once daily versus the same daily dose of telmisartan for 8 weeks, the incidence of drug-related adverse events was numerically higher with the fixed-dose combination than with telmisartan monotherapy (13.8% vs 8.4%[35] and 9.3% vs 7.8%;[34] statistical analysis not reported in either trial). Overall, there were few notable differences in the incidence of specific adverse events between treatment groups.[34,35] Dizziness was reported by 5.6% and 1.8% of once-daily telmisartan/HCTZ 40 mg/12.5 mg and telmisartan 40 mg recipients, respectively, although the difference was not statistically significant (p = 0.081).[35] Once-daily administration of telmisartan/HCTZ 80 mg/12.5 mg was associated with a significantly higher incidence of diarrhoea (4.1% vs 0%; p = 0.002) and a significantly lower incidence of oedema (0.8% vs 3.7%; p = 0.04) and bronchitis (0% vs 2.9%; p = 0.008) than telmisartan 80 mg.[34]

In large comparative trials between telmisartan/HCTZ and other ARBs in combination with HCTZ (section 3.2), tolerability profiles were similar between treatment groups.[45,46,50] The proportion of patients who reported at least one adverse event (regardless of causality) in an 8-week, randomized, double-blind, placebo-controlled, noninferiority trial was 43% with telmisartan/HCTZ 80 mg/25 mg once daily, 38% with valsartan/HCTZ 160 mg/25 mg once daily and 49% with placebo.[45] Aside from minor changes in laboratory parameters (e.g. reduction in serum sodium or potassium levels or increases in uric acid), which were more common with active treatment than with placebo and a numerically higher incidence of headache with placebo than with either telmisartan/HCTZ or valsartan/HCTZ (11.9% vs 3.7% and 6.2%), there were few notable differences between treatment groups for specific adverse events.[45] Similar tolerability data were reported in a subsequent confirmatory trial, although the incidence of headache was similar among the three groups.[46] In this analysis, the ten most frequently observed adverse events occurred in 0.2–3.6% of patients in the telmisartan/HCTZ group, 0.2–4.0% of those in the valsartan/HCTZ group and 2.3–3.1% of those in the placebo group. Dizziness and headache were the most common adverse events in the active treatment groups.[46]

Pooled data[50] from two 6-week randomized trials[48,49] comparing once-daily regimens of telmis-

artan/HCTZ 40 mg/12.5 mg and 80 mg/12.5 mg with once-daily regimens of losartan/HCTZ 50 mg/12.5 mg showed that treatment-related adverse events occurred in 6.4% and 6.3% of patients in the respective telmisartan/HCTZ groups compared with 3.5% of those who received the fixed-dose combination of losartan/HCTZ (statistical analysis not reported).[50] The most frequently reported adverse events in any group were headache and dizziness, although there were no statistically significant differences between the combined telmisartan/HCTZ group and the losartan/HCTZ group.

Tolerability data from other large comparative trials (section 3.3) were generally favourable for telmisartan/HCTZ.[22,23,52] In elderly patients (aged ≥60 years) with systolic hypertension, the overall incidence of adverse events (41.2% vs 53.7%; $p < 0.0001$), the incidence of treatment-related adverse events (8.0% vs 33.4%; $p < 0.0001$) and the rate of discontinuation because of adverse events (5.0% vs 11.3%; $p < 0.0001$) were significantly lower with telmisartan 40–80 mg/12.5 mg once daily than with amlodipine/HCTZ 5–10 mg/12.5 mg once daily.[52] In particular, peripheral oedema occurred in 1.2% of those in the telmisartan/HCTZ group compared with 24.3% of those in the amlodipine/HCTZ group. Patients received 8 weeks of treatment with telmisartan or amlodipine monotherapy followed by 6 weeks of combination therapy with HCTZ, and all values represent adverse events that occurred at any stage of the trial (i.e. with monotherapy or in combination with HCTZ).[52] Telmisartan/HCTZ 80 mg/12.5 mg once daily for 12 weeks was associated with a numerically lower rate of ankle oedema than nifedipine GITS 60 mg once daily (1.6% vs 13.8%)[22] and, unlike the comparator, telmisartan/HCTZ was not associated with sympathetic activation (section 2.1).

5. Dosage and Administration

Fixed-dose combinations of telmisartan/HCTZ (40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg) are available for once-daily oral administration in patients with essential hypertension not adequately controlled by telmisartan monotherapy (US[17] and EU[18] labelling) or HCTZ monotherapy (US labelling[17]). The 80 mg/25 mg tablet has been available in the US for some time[17] and has recently received marketing approval in the EU.[56] Telmisartan/HCTZ may be taken with or without food, and individual dose titration with each of the two components is generally recommended before changing to the fixed-dose combination, although a direct change from monotherapy to the fixed-dose combination may be appropriate for some patients.[17,18]

No dosage adjustments of telmisartan/HCTZ are necessary in elderly patients.[17,18] Dosage adjustments of telmisartan/HCTZ are also not necessary in patients with mild to moderate impairment of renal function.[17,18] However, severe renal impairment (CL_{CR} <30 mL/min) is a contraindication in EU summary of product characteristics.[18] US prescribing information states that loop diuretics are preferred to thiazides in patients with CL_{CR} <30 mL/min and, therefore, the use of telmisartan/HCTZ is not recommended in these patients.[17]

Telmisartan/HCTZ is contraindicated in patients with severe hepatic impairment, cholestasis or biliary obstructive disorders, according to EU summary of product characteristics.[18] US prescribing information[17] states that telmisartan/HCTZ is not recommended for patients with severe hepatic impairment, but advises that patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the relatively low starting dosage of telmisartan/HCTZ 40 mg/12.5 mg once daily.

Volume- or salt-depletion should be corrected prior to administration of telmisartan/HCTZ.[17,18] Concomitant use of telmisartan/HCTZ and lithium is generally not recommended (section 2.2.4). Telmisartan/HCTZ is contraindicated in the second and third trimesters of pregnancy (a boxed warning appears in US prescribing information), as drugs that affect the RAS can cause injury or death to the developing fetus.[17,18] US prescribing information also suggests that the fixed-dose combination should be discontinued as soon as possible after pregnancy is detected.[17] This recommendation is supported by results of an epidemiological study

showing an association between exposure to ACE inhibitors during the first trimester of pregnancy and the risk of congenital malformations,[57] suggesting that it may be necessary to avoid treatment with any RAS blocking drugs, including ARBs, throughout the entire pregnancy.[58]

Local prescribing information should be consulted for detailed information on contraindications, precautions, drug interactions and use of telmisartan/HCTZ in special patient populations.

6. Place of Telmisartan/Hydrochlorothiazide in the Management of Hypertension

The majority of patients with hypertension will require combination therapy with at least two antihypertensive drugs in order to achieve BP goals advocated in international guidelines.[1,6] BP targets are <140/90 mmHg in patients with uncomplicated hypertension and <130/80 mmHg in those with diabetes or other complications such as chronic kidney disease, stroke or myocardial infarction.[1,6] JNC-7 guidelines also recommend combination therapy (including a thiazide diuretic) for patients whose BP is 20/10 mmHg above goal.[1]

For most patients with hypertension, current treatment guidelines recommend thiazide diuretics, alone or in combination with other antihypertensive agents, as initial therapy.[1,6] The role of thiazide and thiazide-like diuretics in hypertension was strengthened by findings from ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), which showed lower rates of major cardiovascular endpoints with chlorthalidone than with an ACE inhibitor and lower rates of heart failure than with a dihydropyridine calcium channel antagonist.[14] These results suggested that thiazide diuretics should be used as first-line drug therapy and as a component of all multidrug antihypertensive regimens if possible. Although more recent data from ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm)[59,60] and ACCOMPLISH (Avoiding Cardiovascular Events in Combination therapy in Patients Living with Systolic Hypertension)[61,62] suggest that the combination of a renin-angiotensin antagonist and a calcium channel antagonist may provide the greatest prevention of cardiac outcomes, current treatment guidelines continue to advocate a thiazide diuretic as part of combination regimens.[1,6]

In particular, combining an ARB (such as telmisartan) with a thiazide diuretic (such as HCTZ) is a rational treatment option, as these agents have complementary mechanisms of action (section 2.1). Moreover, such combinations are not only effective at reducing BP and generally well tolerated when used together, but thiazide diuretics and ARBs have both been shown to have beneficial effects on major clinical outcomes in patients with hypertension (section 1). In addition, recent data from ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial),[63] the largest ARB endpoint trial conducted to date (>150 000 patient-years of data[64]), showed that telmisartan was noninferior to ramipril in reducing mortality and morbidity from cardiovascular causes in patients with vascular disease or high-risk diabetes.[63] Telmisartan was also associated with less angioedema and cough, but more hypotensive symptoms, than ramipril.[63] The combination of telmisartan and ramipril was associated with increased adverse events, but no increase in clinical benefits, relative to monotherapy with either agent alone.[63]

Several large, well designed clinical trials have demonstrated the antihypertensive efficacy of once-daily telmisartan/HCTZ (section 3). Adverse events with telmisartan/HCTZ in clinical trials were typically mild and transient, and no unexpected events occurred that had not been previously reported with either telmisartan or HCTZ (section 4).

Two randomized, double-blind trials showed that the addition of HCTZ 12.5 mg/day to telmisartan 40 or 80 mg/day in nonresponders to telmisartan monotherapy achieved significant BP reductions compared with continued treatment with telmisartan alone (section 3.1). The phase IV MICCAT2 trial also showed that the use of telmisartan/HCTZ in nonresponders to telmisartan monotherapy was

associated with additional BP-lowering efficacy and attainment of JNC-7 and ambulatory BP-based goals in the community practice setting (section 3.1.1). Longer-term data from other trials indicate that the antihypertensive efficacy of telmisartan/HCTZ was maintained for up to 4 years (section 3.1).

Both telmisartan/HCTZ 80 mg/25 mg and valsartan/HCTZ 160 mg/25 mg once daily for 8 weeks produced marked reductions in BP compared with placebo in a randomized, double-blind, noninferiority trial and a subsequent confirmatory study in patients with stage 1 or 2 hypertension (section 3.2.1). Both trials also showed small but significantly greater adjusted reductions in mean seated trough DBP and SBP (primary endpoint) among patients in the telmisartan/HCTZ group than in the valsartan/HCTZ group. Results of these trials may be particularly relevant because the higher-dose formulation of telmisartan/HCTZ 80 mg/25 mg has recently been approved for marketing in the EU,[56,65] and the use of higher doses of thiazide diuretics (e.g. HCTZ 25 mg) in combination with other antihypertensive agents is becoming re-established as an effective and well tolerated treatment strategy to improve control of BP.[38,45,46,53,66] The fixed-dose combination of telmisartan/HCTZ 80 mg/25 mg has been available in the US for some time.[17]

Once-daily administration of telmisartan/HCTZ 80 mg/12.5 mg achieved significantly greater effects on early morning and 24-hour ambulatory BP than valsartan/HCTZ 160 mg/12.5 mg (section 3.2.1), and telmisartan/HCTZ 40 mg/12.5 mg and 80 mg/12.5 mg were associated with significantly greater reductions in early morning ambulatory DBP than losartan/HCTZ 50 mg/12.5 mg in randomized, open-label (blinded-endpoint) trials in patients with mild to moderate hypertension (section 3.2.2). Other randomized, open-label (blinded-endpoint) trials comparing telmisartan/HCTZ 80 mg/12.5 mg once-daily with antihypertensive agents other than ARBs showed statistically significant advantages for telmisartan/HCTZ with respect to various ABPM parameters (section 3.3). For example, significant advantages (for 24-hour, daytime and night-time SBP and DBP) were demonstrated for telmisartan/HCTZ compared with lisinopril/HCTZ 20 mg/12.5 mg in elderly hypertensive patients.

BP control over the entire 24-hour dosage interval, particularly in the early morning period, is a desirable feature of antihypertensive regimens.[67] The circadian rhythm of BP includes a reduction at night-time during sleep,[1,67] followed by a steep rise during the early morning period, and these peak BP levels coincide with a period of increased risk of cardiovascular event onset.[67] In addition, individuals whose BP does not decrease by 10–20% during the night may be at increased risk for cardiovascular events.[1] Several clinical trials with telmisartan/HCTZ measured BP using ABPM (a more accurate prognostic indicator than single clinic BP measurements[67]) and showed that the fixed-dose combination provided consistent 24-hour BP reductions throughout morning, daytime and night-time periods (section 3). In many cases, ambulatory BP reductions were greater with telmisartan/HCTZ than with comparator agents, although absolute differences were not large. However, even small differences in BP reductions between antihypertensive regimens can provide important reductions in cardiovascular risk in large clinical populations.[68] Thus, the statistically significant but modest differences in clinic or ambulatory BP measurements favouring telmisartan/HCTZ in several comparative trials are of clinical relevance.

To date, there do not appear to be any published pharmacoeconomic analyses with fixed-dose combinations of telmisartan/HCTZ. Economic modelling, using data from relatively short clinical trials and projecting longer-term outcomes and costs, would be of potential interest to determine the cost effectiveness of fixed-dose combinations of telmisartan/HCTZ compared with other antihypertensive regimens, including other fixed-dose combinations.

In conclusion, the antihypertensive efficacy of once-daily telmisartan/HCTZ has been demonstrated in several large, randomized trials in patients with stages 1 and 2 hypertension. The addition of HCTZ to telmisartan achieved significant reductions in BP in nonresponders to telmisartan monotherapy,

and the antihypertensive efficacy of telmisartan/HCTZ was similar to or significantly greater than that of various comparator agents. Moreover, in studies that used ambulatory BP monitoring, telmisartan/HCTZ provided consistent 24-hour BP reductions throughout morning, daytime and night-time periods. The BP-lowering efficacy over the entire 24-hour dose administration interval is consistent with the pharmacokinetic profile of telmisartan, which has the longest elimination half-life among currently available ARBs and a unique chemical structure. Adverse events with telmisartan/HCTZ in clinical trials were typically mild and transient, and no unexpected events occurred that had not been previously reported with either telmisartan or HCTZ. Extensive tolerability data are available for telmisartan, in particular from the ONTARGET study, the largest clinical outcomes trial with an ARB. As such, fixed-dose combinations of telmisartan/HCTZ provide an effective, rational and generally well tolerated treatment option for the management of patients with hypertension.

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