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Telmisartan

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Contents

Abstract

▲ Telmisartan is a nonpeptide angiotensin II receptor antagonist which selectively and insurmountably inhibits the angiotensin II AT_1 receptor subtype without affecting other receptor systems involved in cardiovascular regulation.

▲ Oral telmisartan dose-dependently reduced blood pressure (BP) in various animal models of hypertension. In transgenic rats, telmisartan reduced cardiac hypertrophy and glomerulosclerosis.

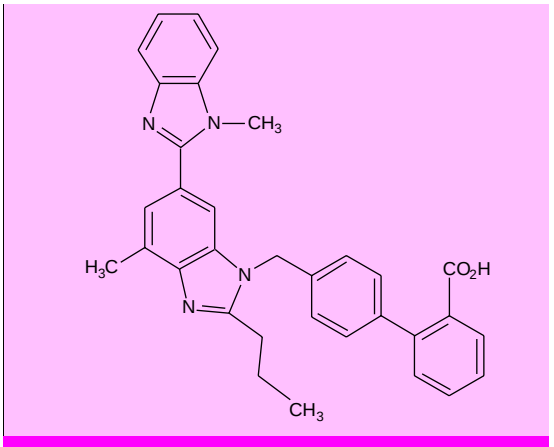
▲ When administered at dosages of 40 to 160mg once daily to patients with mild to moderate hypertension, telmisartan significantly reduced systolic and diastolic BP compared with placebo and was at least as effective as atenolol 50 or 100mg and lisinopril 10 to 40mg. One study showed telmisartan 80 mg/day to be more effective than enalapril 20 mg/day.

▲ In 2 studies that used ambulatory BP monitoring, once daily telmisartan provided better control of diastolic BP for the full dosing interval than losartan potassium 50mg or amlodipine 5 or 10mg.

▲ In a single study in patients with severe hypertension, a telmisartan-based regimen had antihypertensive efficacy similar to that of an enalapril-based regimen.

▲ Telmisartan had a tolerability profile similar to that of placebo in clinical studies.

Features and properties of telmisartan (BIBR 277)	
Indication	
Hypertension	
Mechanism of action	
Angiotensin II receptor antagonist	
Dosage and administration	
Dosage in clinical trials	20 to 160 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile	
Peak plasma concentration	44.7 μg/L (40mg dose)
Time to peak plasma concentration	≈1h
Area under the plasma concentration-time curve	491 μg/L • h (40mg dose)
Bioavailability	43%
Plasma protein binding	>99%
Biotransformation	Minimal
Excretion	Faeces (>98%)
Elimination half-life	≈24h (20 to 160mg dose)
Adverse events	
Telmisartan has a tolerability profile similar to that of placebo	



Telmisartan

The peptide hormone angiotensin II is a primary effector of the renin-angiotensin system (RAS) and as such has potent pressor activity. ACE inhibitors block the formation of angiotensin II and are effective in the treatment of hypertension. However, in addition to blocking the RAS they may disrupt bradykinin, tachykinin and prostaglandin biosynthesis and metabolism. Angiotensin II receptor antagonists provide more specific blockade of angiotensin II at the receptor level and are expected to have an improved tolerability profile compared with ACE inhibitors. Telmisartan is an angiotensin II receptor antagonist which has been developed for the treatment of hypertension.

1. Pharmacodynamic Profile

In Vitro Studies

• Telmisartan has demonstrated selectivity for the angiotensin AT_1 receptor subtype *in vitro*. The drug competitively inhibited binding of [^{125}I]-angiotensin II to AT_1 receptors in rat lung tissue [inhibition constant (K_i) 3.7 nmol/L] but did not affect binding of radiolabelled angiotensin II to AT_2 receptors in isolated rat adrenal medulla (K_i >10 000 nmol/L).[1] Notably, the AT_1-inhibitory effect of telmisartan was ≈6-fold that of losartan potassium (K_i 3.7 *vs* 23.7 nmol/L).[1] Receptor binding of other peptide (e.g. endothelin) or nonpeptide (e.g. acetylcholine and catecholamines) ligands involved in cardiovascular regulation was not affected by telmisartan.[1]

• Telmisartan demonstrated insurmountable and reversible inhibition of angiotensin II–induced contractions in isolated rabbit aortic tissue, with a dissociation constant of 0.33 nmol/L.[1]

Animal Studies

• In anaesthetised pithed rats, intravenous telmisartan 0.1 to 1.0 mg/kg dose-dependently shifted the angiotensin II dose-response curve to the right in a non-parallel manner.[1] The same doses of telmisartan also dose-dependently attenuated the pressor response to intravenous angiotensin II (0.1 μg/kg) in anaesthetised rats and maintained a significant inhibitory effect for at least 2 hours.[1]

• Orally administered telmisartan significantly and dose-dependently reduced blood pressure (BP) in various experimental models of hypertension, including renovascular hypertensive rats,[1,2] spontaneously hypertensive rats,[2,3] conscious sodium-depleted cynomolgus monkeys[4] and transgenic rats.[5]

• Orally (0.3 to 3.0 mg/kg/day) or intravenously (0.03 to 0.3 mg/kg/day) administered telmisartan caused diuresis and natriuresis in conscious dogs but did not affect potassium or creatinine excretion.[6]

• Nine weeks' treatment with antihypertensive (1 and 3 mg/kg/day) or non-antihypertensive (0.1 mg/kg/day) doses of oral telmisartan significantly reduced cardiac hypertrophy in transgenic rats compared with untreated controls as assessed by heart weight and cardiac muscle bundle diameter.[7] Furthermore, the severe glomerulosclerosis and proteinuria evident in untreated control animals was not observed in telmisartan-treated animals.[8]

Volunteer Studies

• Single oral doses of telmisartan 20, 40 and 80mg dose-dependently inhibited the pressor response to an angiotensin II challenge in a randomised, double-blind, placebo-controlled study involving

48 healthy male volunteers.[9] Inhibition was near maximal with the 40mg dose, and at this dose the drug had an onset and duration of action of 0.3 and 35.4 hours, respectively, suggesting that once daily treatment is feasible. Diuresis and natriuresis increased significantly and dose-dependently in the first 3 hours after drug administration. Aldosterone and noradrenaline levels were unaffected by telmisartan, but compensatory increases in plasma angiotensin II levels and plasma renin activity occurred.

2. Pharmacokinetic Profile

• A single oral dose of [^{14}C]-radiolabelled telmisartan 40mg was rapidly absorbed by 5 healthy volunteers; peak plasma concentrations (C_{max}; 44.7 μg/L) were reached 1 hour (median) [t_{max}] after drug administration.[10]

• Steady-state plasma concentrations were reached within 7 days in 228 patients with mild to moderate hypertension treated with telmisartan 20 to 160 mg/day for 4 weeks.[11]

• The area under the plasma telmisartan concentration-time curve was 491 μg/L · h after a 40mg oral dose in volunteers; the mean residence time was 17.0 hours.[10]

• A comparison of the absorption of oral and intravenous telmisartan in 10 volunteers showed telmisartan to have an absolute bioavailability of 43%.[10]

• Telmisartan undergoes minimal biotransformation. After a radiolabelled 40mg oral dose in healthy volunteers, 84% of the total radioactivity in plasma was attributed to unchanged parent compound.[10]

• Plasma protein binding of telmisartan was >99% in 10 healthy male volunteers.[10,12] In rats, the highest concentration of [^{14}C]-radiolabelled telmisartan was found in the liver, with lower levels in the blood, renal cortex and myocardium. Little of the drug was distributed to the brain.[12]

• The mean elimination half-life ($t_{1/2}$) of telmisartan was ≈24 hours in 228 patients with mild to moderate hypertension who received telmisartan 20 to 160 mg/day for 4 weeks.[11]

• Virtually all (>98%) of an oral dose of telmisartan 40mg was excreted in the faeces in healthy volunteers;[10,13] the remainder was recovered in the urine.[10] Most (>90%) of an oral or intravenous telmisartan dose was recovered within 120 hours.[10]

Drug Interactions

• The pharmacokinetics of telmisartan 120 mg/day were not influenced by coadministration of warfarin in 12 healthy male volunteers.[14] In contrast, trough plasma concentrations of warfarin were significantly reduced during coadministration of telmisartan, although coagulation parameters were unaffected.[14]

• In a multiple dose study involving 12 healthy volunteers, telmisartan caused a variable increase in digoxin serum levels. Plasma digoxin concentrations should therefore be monitored in patients taking this combination (data on file, Glaxo Wellcome).

3. Therapeutic Trials

Comparison with Placebo

• In a multicentre, randomised, double-blind study involving 274 patients with mild to moderate hypertension, 4 weeks' treatment with telmisartan 40 to 160mg once daily significantly reduced supine diastolic and systolic BP compared with placebo ($p < 0.05$) [fig. 1] without significantly affecting heart rate.[11] BP reductions achieved with telmisartan 40 and 80 mg/day were close to those seen with higher dosages. Significant reductions in diastolic BP were reported with all telmisartan dosages within 1 week and were maintained for the duration of the study. At study end, trough/peak ratios for diastolic BP were ≥84% with all telmisartan dosages and trough/peak ratios for systolic BP were ≥66% with telmisartan dosages ≥40 mg/day, thus confirming the sustained efficacy of the drug over a 24-hour dosing period.[11]

Comparisons with a β-Blocker

• Telmisartan (40 to 120 mg/day) and atenolol (50 or 100 mg/day) demonstrated similar antihyper-

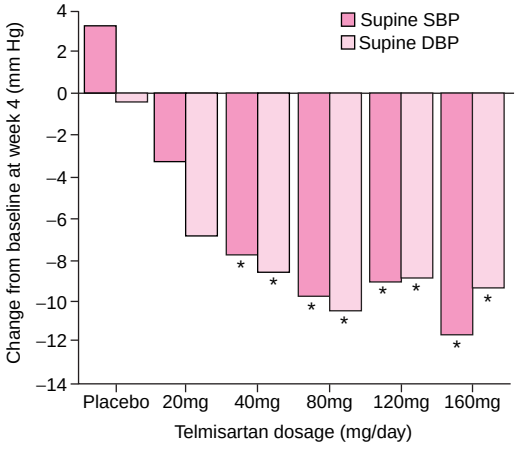


Fig. 1. Antihypertensive effects of telmisartan in patients with mild to moderate hypertension. Patients were randomised to receive placebo (n = 46) or telmisartan 20mg (n = 47), 40mg (n = 47), 80mg (n = 44), 120mg (n = 45) or 160mg (n = 44) once daily for 4 weeks in a double-blind manner. **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure.[11] * $p < 0.05$ *vs* corresponding placebo value.

tensive efficacy during an 8-week double-blind placebo-controlled study involving 236 patients with mild to moderate hypertension[15] and after a longer period of treatment (26 weeks) in 533 patients who also had mild to moderate hypertension.[16] In the latter study, supine diastolic BP was ≤90mm Hg and/or reduced by ≥10mm Hg from baseline in 84% of telmisartan compared with 78% of atenolol recipients at study end (34 and 29% of patients in each group required concomitant hydrochlorothiazide to achieve BP control).[16]

Comparisons with ACE Inhibitors

• Telmisartan 40 to 160mg was as effective as lisinopril 10 to 40mg after once daily administration for ≈1 year in patients with mild to moderate hypertension treated in a randomised, double-blind manner.[17] 74% of telmisartan and 72% of lisinopril recipients had diastolic BP <90mm Hg at the end of the 4- to 12-week titration period; 45 and 43% of patients in each treatment group, respectively, achieved BP control with the initial dosage (40 mg/day for telmisartan and 10 mg/day for lisinopril). In patients who were observed for ≥39 weeks after dosage titration, trough BP was reduced by 22/17mm Hg with telmisartan (n = 221) and by 19/16mm Hg with lisinopril (n = 116). The addition of hydrochlorothiazide 12.5 or 25 mg/day improved the BP-lowering effects of telmisartan in patients with low plasma renin activity (<0.8 ng/ml/h).[17]

• Telmisartan was at least as effective as enalapril in patients with varying degrees of hypertension who were randomised to either treatment.[18,19] In 440 patients with mild to moderate hypertension, all dosages of telmisartan (40, 80, 120 and 160mg) and the one dosage of enalapril studied (20mg) significantly reduced supine BP compared with placebo when administered once daily in a double-blind manner for 12 weeks ($p \leq 0.001$).[18] Reductions in supine BP at week 12 were significantly greater with telmisartan 80 mg/day than with enalapril 20 mg/day ($p \leq 0.03$).[18] In patients with severe hypertension treated in a nonblind manner for 8 weeks, 27 of 57 (47%) of those who received a telmisartan 80 or 160 mg/day regimen and 9 of 28 (32%) who received an enalapril 20 or 40 mg/day regimen had supine diastolic BP <90mm Hg at study end (fig. 2).[19] However, 72 and 71% of responders in the respective groups achieved this BP reduction only after the addition of hydrochlorothiazide 25 mg/day, and 33 and 21% of responders, respectively, required the addition of both hydrochlorothiazide and amlodipine 5 mg/day.[19]

Comparison with an Angiotensin II Receptor Antagonist

• In a randomised, double-blind study involving 207 patients with mild to moderate hypertension,[20] treatment with telmisartan 40 or 80 mg/day or losartan potassium 50 mg/day for 6 weeks significantly reduced 24-hour ambulatory BP compared with placebo. However, both dosages of telmisartan reduced systolic and diastolic BP during the final 6 hours of the dosing interval significantly more effectively than losartan potassium ($p \leq 0.05$).

Comparison with a Calcium Antagonist

• Telmisartan 40 to 120 mg/day had efficacy similar to that of the calcium antagonist amlodipine 5 or 10 mg/day in a placebo-controlled study involving 185 patients with mild to moderate hypertension.[21] At study end, mean 24-hour ambulatory BP was reduced by 18/11mm Hg in telmisartan recipients and by 16/9mm Hg in amlodipine recipients (both $p < 0.05$ *vs* placebo). Both agents also significantly reduced daytime and night-time BP and therefore maintained their antihypertensive efficacy throughout the dosing interval. However, telmisartan was more effective than amlodipine at reducing diastolic BP over the last 4 hours of the dosing interval ($p < 0.05$).

4. Tolerability

• Telmisartan 20 to 160 mg/day was as well tolerated as placebo in 274 patients with mild to moderate hypertension treated for 4 weeks; the total incidence of treatment-emergent adverse events in each group was 30.3 and 30.4%, respectively.[11] The most common treatment-related adverse events associated with telmisartan and placebo were headache (1.3 *vs* 2.2%) and dizziness (1.8 *vs* 0%).[11] The majority of adverse events in telmisartan recipients were of mild to moderate severity and their incidence was not related to dose.

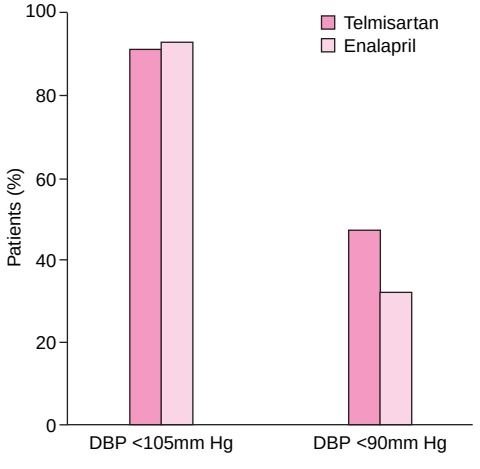


Fig. 2. Comparative efficacy of telmisartan and enalapril in patients with severe hypertension. Evaluable patients were randomised to receive telmisartan 80mg (n = 57) or enalapril 20mg (n = 28) once daily for 7 or 8 weeks in an open-label manner. Dosages were doubled after 1 week if DBP remained ≥115mm Hg or after 2 weeks if DBP remained ≥90mm Hg. Hydrochlorothiazide 25 mg/day and amlodipine 5 mg/day were added in a stepwise manner at weeks 3 or 4 if necessary.[19] **DBP** = diastolic blood pressure.

• Telmisartan 40 to 120 mg/day was as well tolerated as atenolol 50 or 100 mg/day in 2 comparative studies involving a total of 769 patients with mild to moderate hypertension treated for 12[15] or 26[16] weeks. Impotence and fatigue were reported more often with atenolol (4.0 and 3.4%, respectively) than with telmisartan (1 and 0.8%) in the latter study.[16]

• No significant between-group differences were observed in the type, incidence and severity of adverse events reported in 86 patients with severe hypertension who received telmisartan (80 or 160mg) or enalapril (20 or 40mg) once daily for up to 8 weeks.[19] In 440 patients with mild to moderate hypertension treated for 12 weeks, however, the incidence of treatment-related events was lower in telmisartan (7.5%) than in enalapril (13.9%) or placebo (10.5%) recipients.[18]

• The long term tolerability of telmisartan 40 to 160 mg/day was better than that of lisinopril 10 to 40 mg/day in a study involving 578 patients with mild to moderate hypertension treated for ≈1 year (28 *vs* 40% of patients in each group reported treatment-related events; $p = 0.001$) [fig. 3].[17] Notably, the incidence of cough was significantly lower with telmisartan than with lisinopril (3 *vs* 7%; $p = 0.018$) [fig. 3] in this study[17] and in a study involving 88 patients with a history of ACE inhibitor cough (16 *vs* 60%; $p = 0.001$).[22] In the latter study, the incidence of cough in telmisartan 80mg recipients (16%) was not significantly different from that in placebo recipients (10%).

• Telmisartan 40 to 160 mg/day had no clinically significant effects on glucose or lipid metabolism in patients treated for 12 weeks.[18]

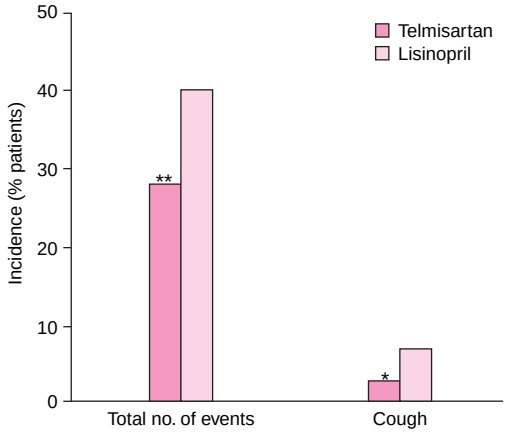


Fig. 3. Total incidence of adverse events and cough associated with long term telmisartan and lisinopril. Patients with mild to moderate hypertension were randomised to receive telmisartan 40 to 160mg (n = 385) or lisinopril 10 to 40mg (n = 193) once daily for ≈1 year in a double-blind manner.[17] * p = 0.018, ** p = 0.001 *vs* lisinopril.

5. Telmisartan: Current Status

Telmisartan is an angiotensin II receptor antagonist which has shown clinical efficacy in patients with varying degrees of hypertension and is well tolerated.

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