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Candesartan Cilexetil plus Hydrochlorothiazide Combination

A Review of its Use in Hypertension

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Data Selection

Sources: Medical literature published in any language since 1980 on candesartan-cilexetil/hydrochlorothiazide, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 search terms were 'candesartan cilexetil hydrochlorothiazide'. EMBASE search terms were 'candesartan cilexetil hydrochlorothiazide'. AdisBase search terms were 'candesartan cilexetil hydrochlorothiazide'. Searches were last updated 28 February 2002.

Selection: Studies in patients with hypertension who received candesartan cilexetil plus 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: Hypertension, candesartan cilexetil, hydrochlorothiazide, blood presure, angiotensin II type 1 receptor inhibitor, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

The combination of candesartan cilexetil [an angiotensin II type 1 (AT_1) receptor antagonist] plus hydrochlorothiazide (a thiazide diuretic), has been used in the treatment of patients with hypertension. The blood pressure (BP) lowering effect of various doses of this combination, administered orally once a day for 4 to 52 weeks, has been demonstrated in clinical trials. These studies showed that combinations of candesartan cilexetil 4 to 16mg with hydrochlorothiazide 12.5 or 25mg induced significant reductions in systolic (S) BP and diastolic (D) BP from baseline in patients with mild to severe hypertension.

Data from clinical trials indicated that reductions in BP induced by candesartan cilexetil 4 to 32mg/hydrochlorothiazide 12.5mg combinations were significantly greater than those observed after monotherapy with either drug. Treatment for 8 weeks with candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg or candesartan cilexetil 16mg induced SBP/DBP reductions of 12.0/7.5mm Hg and 7.5/5.5mm Hg, respectively ($p < 0.05$ both comparisons). Moreover, data from a randomised, double-blind, placebo-controlled, dose-finding study in 1038 patients with mild to moderate hypertension showed that the greatest reductions in SBP/DBP were achieved by candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg. Significant differences in BP reduction in favour of the combination were observed when hypertensive patients were given candesartan cilexetil 4 or 8mg/hydrochlorothiazide 12.5mg or hydrochlorothiazide monotherapy for 8 weeks. Additionally, greater efficacy of the combination compared to monotherapy with either drug was demonstrated by response rates to treatment. Moreover, a fixed combination of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg demonstrated a greater antihypertensive effect than losartan 50mg/hydrochlorothiazide 12.5mg in two clinical trials. Candesartan cilexetil 8mg/hydrochlorothiazide 12.5mg showed a similar antihypertensive effect compared with that of combined lisinopril 10mg/hydrochlorothiazide 12.5mg.

Candesartan cilexetil/hydrochlorothiazide combination therapy was well tol-

erated in patients with hypertension. Combined data from placebo-controlled trials showed that most adverse events were uncommon and not serious. Patients receiving combination therapy exhibited, among other adverse events, headache (3.2 *vs* 5.5% for candesartan cilexetil/hydrochlorothiazide and placebo, respectively), back pain (3.0 *vs* 2.4%), dizziness (2.6 *vs* 1.2%) and respiratory infection (2.5 *vs* 1.4%). Moreover, 3.3 and 2.7% of patients receiving candesartan cilexetil/hydrochlorothiazide or placebo, respectively, discontinued treatment because of adverse events.

Conclusion: The combination of candesartan cilexetil and hydrochlorothiazide (AT_1 receptor antagonist and thiazide diuretic, respectively) is an effective treatment for patients with hypertension. Data from randomised, double-blind, placebo-controlled clinical trials showed that this combination is significantly more efficacious than either agent alone. Moreover, the combination of these two agents showed an excellent adverse event profile. Current data support the use of this combination as an alternative when monotherapy with either agent is not effective, and there are no compelling or specific indications for other drugs. However, data from large clinical trials, evaluating morbidity and mortality outcomes, are needed to determine the precise role of candesartan cilexetil/hydrochlorothiazide combination in the treatment of patients with hypertension.

Pharmacodynamic Properties

The pharmacodynamic properties of candesartan cilexetil and hydrochlorothiazide have been studied extensively.

Candesartan cilexetil is rapidly and completely converted to candesartan, the active compound, during absorption in the upper gastrointestinal tract. Candesartan is a nonpeptide angiotensin II receptor antagonist that binds to angiotensin subtype 1 (AT_1) receptors without interacting with AT_2 receptors. Data from animal studies showed that candesartan binding to AT_1 receptors is tight, highly specific and insurmountable, while dissociation from AT_1 receptors is slow. Human studies in healthy volunteers and patients with hypertension showed that candesartan dose-dependently and significantly ($p < 0.05$ *vs* placebo) increased plasma renin activity and plasma angiotensin II levels. This action of candesartan was present 24 hours after administration and increased after repeated doses. Also, *in vivo* inhibition of angiotensin II activity by candesartan (per mg of active drug) was stronger than that shown by losartan, irbesartan, telmisartan or valsartan. The dose required to induce a 2-fold rightward shift in the angiotensin II dose-response curve was 6mg for candesartan cilexetil, 54mg for telmisartan, 123mg for irbesartan and 93.5mg for valsartan. A study reported similar blockade of AT_1 receptors after administration of a single dose of candesartan cilexetil 32mg (a dosage approved only in the US) or losartan 150mg (supratherapeutic dose of losartan) to healthy volunteers. However, the inhibitory action of candesartan cilexetil appeared to be of longer duration than that of losartan (72 *vs* 62% blockade of AT_1 receptors, 24 hours after administration).

In patients with hypertension, candesartan cilexetil 8 or 16mg daily reduced plasma endothelin-1 levels from baseline (2.49 ± 1.32 ng/L) after 2 (1.61 ± 0.88 ng/L, $p < 0.05$) and 12 months (0.72 ± 0.53 ng/L) of treatment. Also, candesartan cilexetil treatment improved vasoconstriction induced by a nitric oxide antagonist.

Candesartan cilexetil 2 to 12mg once daily for up to 24 weeks reduced left ventricular (LV) mass by up to 9.3% in 18 Japanese patients with mild to moderate hypertension. Beneficial effects of candesartan cilexetil therapy on LV hypertro-

phy, diastolic time, peak velocity filling and forearm vascular resistance have also been suggested by recent studies.

Candesartan cilexetil improves/preserves renal function and reduces proteinuria in hypertensive patients with concomitant type 2 diabetes mellitus and/or renal impairment without affecting urinary sodium, potassium or uric acid excretion. In hypertensive patients receiving candesartan cilexetil 16 mg/day for 6 weeks or 4 to 8 mg/day for 2 weeks, glomerular filtration rate was unchanged. Candesartan cilexetil decreased urinary albumin excretion and proteinuria in hypertensive patients with concurrent type 2 diabetes mellitus or renal impairment. The CALM (Candesartan and Lisinopril Microalbuminuria) study (n = 199) indicated that candesartan cilexetil 16mg once a day in hypertensive patients with type 2 diabetes mellitus reduced urinary albumin to creatinine ratio from baseline by 15 to 42% ($p < 0.001$) and 0 to 43% ($p = 0.05$) after 12 or 24 weeks of treatment, respectively.

Thiazides act within the distal tubule of the nephron blocking the transmembrane-coupled Na-Cl transport system. However, despite their wide use and proven efficacy in patients with hypertension, their mechanism of BP reduction is not fully understood. Hydrochlorothiazide treatment significantly reduces mean arterial pressure and the reductions are observed from the first week of therapy. Decreases in cardiac output and stroke volume are detected in the first weeks of treatment but after 24 weeks these parameters return to baseline levels. More importantly, it appears that there are substantial differences between patients who respond to hydrochlorothiazide therapy and those who do not. After up to 36 weeks of treatment only nonresponders showed reductions in cardiac output (≈13%) and heart rate (10%), and increases in total peripheral resistance (≈10 to 12%), whereas responders showed significant reductions in total peripheral resistance (≈12 to 20%, $p < 0.05$).

Data from human studies suggest that hydrochlorothiazide reduces LV mass and size in patients with hypertension. Hydrochlorothiazide 25 to 50mg daily for 6 months significantly reduced septum thickness, posterior wall thickness, left atrium size, LV diastolic dimension and LV mass index compared with baseline values. Reductions in LV mass and left atrial size have been confirmed by a large (n = 1105), long-term (1 to 2 years), randomised, double-blind clinical trial, but not by other studies.

Pharmacokinetic Properties

Candesartan cilexetil is rapidly and completely converted to the active compound candesartan during absorption from the gastrointestinal tract. Candesartan peak plasma concentrations (C_{max}) are reached after ≈3 to 5 hours (t_{max}) of administration and increase dose-dependently. Accumulation of the drug is not observed after repeated administration of candesartan cilexetil and its bioavailability (administered as an oral solution) is 42% that of intravenous administration and is not affected by food intake.

Candesartan is mainly eliminated unchanged, through the urine (33%) and faeces (67%), although a small amount is metabolised to its inactive metabolite, CV 15959. The total plasma clearance of candesartan in hypertensive patients receiving candesartan cilexetil 2 to 16 mg/day for 28 days was calculated to be 14.07 L/h. In healthy volunteers, values of 0.25 and 0.20 L/h/kg on day 1 and day 8, respectively, were calculated after oral administration of candesartan cilexetil 1 to 8 mg/day. The elimination half-life ($t_{½}$) of the drug was 9 to 13 hours and was independent of the dose.

Compared with C_{max} in 19- to 40-year old patients with hypertension, C_{max} increases of up to ≈ 50% were observed in elderly patients. The $t_{½}$ was slightly longer among elderly volunteers but accumulation of the drug was not observed after repeated administration.

Hypertensive patients with renal impairment showed substantial (≥40%) increases of C_{max}, area under the plasma concentration-time curve (AUC) and $t_{½}$ compared with patients with normal kidney functions. These increases were almost 2-fold in those with severe renal impairment (creatinine clearance <1.8 L/h/1.73m^2). The $t_{½}$ was significantly higher in patients with severe renal impairment, after single (12 *vs* 6.7 hours, $p < 0.05$) and multiple dose administration (15.7 *vs* 7.1 hours, $p < 0.01$) than in with patients normal, or mildly impaired renal function.

No significant changes in the pharmacokinetic properties of candesartan were observed after single or repeated administration of candesartan cilexetil 12 mg/day to hypertensive patients with mild to moderate liver impairment. However, compared with healthy volunteers, patients with moderate to severe liver impairment showed increases of AUC and C_{max} of 78 and 64%, respectively, after receiving a single dose of candesartan cilexetil 16mg.

Significant interactions of candesartan with other drugs were not observed. Candesartan is only metabolised to a limited extent by the cytochrome P450 system and inhibitors or inducers of this system are unlikely to interact with candesartan.

Hydrochlorothiazide is not metabolised and is rapidly eliminated by the kidney (≥61% of the dose within 24 hours) in the urine (>95%) as the unchanged drug. After oral administration, C_{max} is observed within 1 to 5 hours, and concentrations of hydrochlorothiazide are greater in whole blood than in plasma. After a 24-hour observation period, plasma $t_{½}$ ranged from 6 to 15 hours. Food intake reduces C_{max} (by 20%) and bioavailability (by 10%), and increases t_{max} (by 1.6 to 2.9 hours). Renal impairment prolongs hydrochlorothiazide $t_{½}$ and increases C_{max}.

Hydrochlorothiazide may interact with alcohol and other agents including barbiturates, narcotics, antidiabetic drugs, cholestyramine and colestipol resins and corticosteroids. Hydrochlorothiazide should not be administered with lithium, since it may cause lithium toxicity.

Therapeutic Use

Data from well designed studies that included patients with mild to severe hypertension have shown that combination of candesartan cilexetil 4 to 16mg with hydrochlorothiazide 12.5 to 25mg administered once daily effectively reduces BP in most patients. Moreover, patients treated with this combination showed significantly greater reductions of BP than those receiving either drug as monotherapy.

In a randomised, double-blind, placebo-controlled, dose-finding study including 1038 hypertensive patients, reductions in systolic (SBP)/diastolic (DBP) blood pressure ranged from 12.9 to 23.0mm Hg/7.2 to 16.6mm Hg after candesartan cilexetil 4, 8 or 16mg/hydrochlorothiazide 12.5 or 25mg administration. Patients receiving candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg showed the greatest reductions in DBP and SBP. Moreover, the percentage of patients who responded to therapy (i.e. sitting DBP was <90mm Hg or was reduced by ≥10mm Hg after treatment) was greater in the combination therapy group (47 to 85%) than in the placebo group (30%; $p < 0.05$).

Candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg demonstrated BP lowering effects superior to those of candesartan cilexetil 16mg monotherapy. Reductions in SBP/DBP and response rates were greater among patients receiving the combination treatment although the proportion of patients who had controlled their BP (DBP <90mm Hg) at treatment endpoint did not differ significantly between treatment groups. Similar superiority of the combination over candesartan cilexetil monotherapy was also observed with the use of candesartan cilexetil 32mg/hydrochlorothiazide 12.5mg or candesartan cilexetil 4mg/hydrochlorothiazide 6.25mg, daily. Moreover, statistically significant differences between combination and monotherapy in SBP/DBP reductions and response rates showed superiority of candesartan cilexetil 4 to 32mg/hydrochlorothiazide 12.5mg treatment over hydrochlorothiazide 12.5mg monotherapy. Add-on candesartan cilexetil 8 or 16mg in patients with severe hypertension, who did not respond to 1 week of hydrochlorothiazide 12.5mg, was also significantly more efficacious than add-on placebo, and this superiority of the combination was confirmed in a subset of Black patients.

The antihypertensive effect of candesartan cilexetil/hydrochlorothiazide combination has been compared with that of losartan/hydrochlorothiazide and lisinopril/hydrochlorothiazide. Data from randomised, double blind studies in patients with mild to severe hypertension showed that the antihypertensive effect of candesartan cilexetil/hydrochlorothiazide was greater than that of losartan/hydrochlorothiazide and similar to that of lisinopril/hydrochlorothiazide. These studies used single, fixed, submaximal doses of the combinations tested; it is not clear if the tested doses are therapeutically equivalent dosages.

Tolerability

Combined data from five randomised, double-blind, placebo-controlled clinical trials during preregistration phase, in patients with mild to moderate hypertension receiving candesartan cilexetil/hydrochlorothiazide (up to 16mg/25mg once daily) indicated that adverse events are uncommon and include few of serious nature. Among patients receiving combination therapy (n = 1025) or placebo (n = 526) the incidence of serious adverse events was 1.6 and 2.1%, respectively, and only 3.3 and 2.7% of patients discontinued treatment. The most commonly reported adverse events (cumulative 8-week incidence) were headache (3.2 *vs* 5.5% for candesartan cilexetil/hydrochlorothiazide and placebo, respectively), back pain (3.0 *vs* 2.4%), dizziness (2.6 *vs* 1.2%) and respiratory infection (2.5 *vs* 1.4%). Clinically important changes in laboratory parameters were seldom associated with combination therapy.

Combined tolerability data from placebo-controlled studies, mainly performed in the US, included patients (n = 1089) receiving various candesartan cilexetil/hydrochlorothiazide combinations (2 to 32mg/6.25 to 25mg daily, respectively). Adverse events, regardless of attribution to treatment, reported among combination and placebo recipients, respectively, included respiratory tract infection (3.6 *vs* 3.0%), back pain (3.3 *vs* 2.4%), influenza-like symptoms (2.5 *vs* 1.9%), dizziness (2.9 *vs* 1.2%) and headache (2.9 *vs* 5.2%). Hypokalaemia was observed in at least 0.5% of patients worldwide.

The incidence of adverse events during candesartan cilexetil/hydrochlorothiazide treatment was similar to that of losartan/hydrochlorothiazide or lisinopril/hydrochlorothiazide treatment. However, compared with candesartan cilexetil/hydrochlorothiazide recipients, the incidence of cough appeared higher among patients receiving lisinopril/hydrochlorothiazide (4.6 *vs* 23.1%).

Dosage and Administration

Candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg is the most commonly recommended dosage of the fixed combination in the US and Europe. In the US and Europe, a combination tablet of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg is available for patients in whom adequate BP control is not achieved with candesartan cilexetil 16 mg/day, and in the US a candesartan cilexetil 32mg/hydrochlorothiazide 12.5mg combination tablet is recommended in patients whose BP is not controlled by candesartan cilexetil 32 mg/day. Candesartan cilexetil 8mg/hydrochlorothiazide 12.5mg is available in some European countries.

Use of the combination in patients with severe renal impairment is not recommended and is contraindicated in pregnant women. Hypertensive patients with hepatic function deficiency should be monitored during candesartan cilexetil/hydrochlorothiazide treatment.

1. Introduction

A diagnosis of hypertension is made after at least two diastolic (DBP) or systolic blood pressure (SBP) measurements ≥90 or ≥140mm Hg, respectively.[1] This is an arbitrary definition needed for practical reasons, since no specific values of BP have been identified where cardiovascular and other complications occur. Interestingly, a large (n = 18 790), prospective, randomised study [the Hypertension Optimal Treatment (HOT) study] demonstrated maximum benefits, regarding incidence of cardiovascular events, from lowering SBP to 130 to 140mm Hg and DBP to 80 to 85mm Hg.[2] In this study the lowest incidence of major cardiovascular events occurred at a mean SBP/DBP value of 138.5/82.6mm Hg and the lowest risk of cardiovascular mortality was achieved at 138.8/86.5 mm Hg. Further reductions in BP from these values were not associated with an increase of major cardiovascular events; that is, evidence of a J-shaped curve for the relation of these events and BP reductions was not observed. Moreover, in hypertensive patients with diabetes mellitus, DBP values ≤80mm Hg were associated with a 51% reduction in the incidence of cardiovascular events compared with that of patients exhibiting DBP values >80 and ≤90mm Hg ($p < 0.01$).[2]

The renin-angiotensin system (RAS) plays a central role in the regulation of cardiovascular and renal functions.[3] The octapeptide hormone angiotensin II, the end product of the RAS, exerts harmful cardiovascular effects that include vasoconstriction, fluid and sodium retention, myocyte and smooth muscle cell hypertrophy, myocardial and vascular wall fibrosis, and fibroblast hyperplasia. Angiotensin II also stimulates other neurohormonal systems leading to increased release of noradrenaline, endothelin, vasopressin and antidiuretic hormone (aldosterone). It is likely that the combined action of these effects contributes to structural alterations in various organs and to the potent pressor activity of angiotensin II.[3-5] Although two of several subtypes of angiotensin II receptors have been investigated [angiotensin subtype 1 (AT_1) and AT_2], AT_1 receptors appear to mediate all known harmful effects of angiotensin II.[3,4]

Angiotensin converting enzyme (ACE) inhibitors reduce the activity of RAS by competitively preventing the enzymatic cleavage of inactive angiotensin I into active angiotensin II. In clinical settings, ACE inhibitors have shown benefit in the treatment of patients with congestive heart failure and left ventricular dysfunction secondary to myocardial infarction and in patients with proteinuric nephropathy and elevated BP.[6] However, other enzymes, including cathepsin G, human heart chymase, elastase and tissue plasminogen activator, catalyse the conversion of angiotensin I to angiotensin II, so suppression of angiotensin II may be insufficient during ACE inhibitor treatment. Moreover, angiotensin II, through interaction with

AT_2 receptors, may have desirable effects (vasodilation, inhibition of cell growth, inhibition and regression of fibrosis, cell differentiation and tissue repair) which may be reduced by ACE inhibitors.[3]

AT_1 receptor antagonists, such as candesartan, inhibit the RAS by a highly specific blockade of AT_1 receptors with no interference in the actions of angiotensin II mediated through AT_2 receptors. AT_1 receptor antagonists have been shown to effectively reduce BP in clinical trials and together with β-blockers, diuretics, calcium channel antagonists and ACE inhibitors, provide a wide range of drugs for the treatment of patients with hypertension. However, control of hypertension remains suboptimal in many patients,[7-10] partially because of the difficulty of reducing BP to target levels with monotherapy. At the end of the HOT study, 78% of the patients were still receiving felodipine, mostly in conjunction with ACE inhibitors (41%), β-blockers (28%) or diuretics (22%).[2] It was also reported that in this study fewer than 50% of patients achieved target BP when receiving monotherapy,[11] while 92% of the total study population (n=18790 of whom a majority were treated with combination treatment) achieved BP control. Therefore, combination of different antihypertensive drug classes are being increasingly used as initial treatment or in place of monotherapy. Combination therapy, particularly in the case of low-dose combination therapy or combination of drugs from different classes (for example, candesartan cilexetil plus hydrochlorothiazide), with different mechanism of action, may have additive or synergistic effects on BP while also minimising dose-dependent adverse events.[10,12]

Hydrochlorothiazide is a thiazide diuretic that acts within the distal tubule, blocking Na^+Cl^- transport. Agents of this class appear to cause similar benefits in the treatment of patients with hypertension. They induce reductions of DBP similar to that observed among patients receiving β-blockers, calcium channel antagonists, ACE inhibitors, AT_1 receptor antagonists and α-adrenergic blockers. However, data from a meta-analysis indicated that reductions of SBP were significantly greater among patients receiving thiazide diuretics than among recipients of β-blockers, calcium channel antagonists or ACE inhibitors.[13] More importantly, low-dose thiazide diuretics (equivalent to less than 50 mg/day hydrochlorothiazide) have a beneficial effect on the rates of total stroke, coronary arterial disease, total cardiovascular events and mortality, and constitute first-line therapy for most patients with hypertension.[7,13,14]

This review focuses on the clinical use of the combination candesartan cilexetil/hydrochlorothiazide (AT_1 receptor antagonist/diuretic) in the treatment of patients with hypertension. Although a fixed combination tablet is available, this review also includes studies in which the combination was administered as separate tablets.

2. Pharmacodynamic Properties

Apart from its antihypertensive action, the pharmacodynamic properties of the candesartan cilexetil/hydrochlorothiazide combination have not been studied in patients or healthy volunteers. Therefore, the pharmacodynamic properties included in section 2 are from studies in animals, patients and/or healthy volunteers receiving candesartan cilexetil or hydrochlorothiazide as monotherapy.

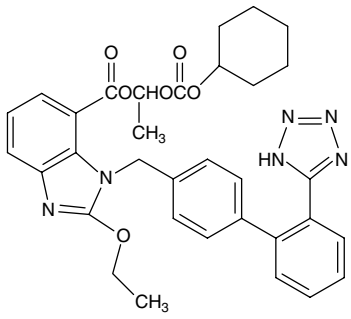
2.1 Candesartan Cilexetil

Candesartan (figure 1) is a nonpeptide angiotensin II receptor blocker that binds with high specificity to AT_1 but not to AT_2 receptors.[15] This drug, administered orally as candesartan cilexetil (figure 1), is rapidly and completely converted to candesartan, the active compound, during absorption from the upper gastrointestinal tract.

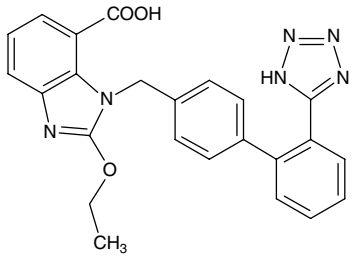
The pharmacodynamic characteristics of candesartan cilexetil have been extensively reviewed (table I).[4,5,15,16] This section provides an overview of candesartan cilexetil pharmacodynamic properties updated with data from recent studies.

2.1.1 Receptor Binding and Inhibition of Angiotensin II Activity

The receptor binding and consequent inhibitory effect of candesartan on angiotensin II activity have been confirmed in human studies.[5,15]



Candesartan cilexetil



Candesartan

Fig. 1. Structural formulae of the prodrug candesartan cilexetil and the active compound candesartan.

In healthy volunteers[43-45] and patients with essential hypertension[27], oral candesartan cilexetil 1 to 8mg (single dose), dose-dependently increased plasma renin activity and plasma angiotensin II concentration, probably an indirect effect of AT_1 receptor blockade. This increase was significant ($p < 0.05$ *vs* placebo) and long-lasting (present 24 hours after drug administration) and was accentuated with repeated doses.

Recent studies with healthy volunteers (n = 8 to 48), indicated that candesartan cilexetil 4 to 32 mg/day for up to 8 days induced a rightward shift of the DBP response curves to exogenously administered angiotensin II[46-48] and efficiently blocked AT_1 receptors.[49] Overall, 24 hours after administration to healthy volunteers, the angiotensin II inhibiting activity per milligram of candesartan cilexetil was stronger than that shown by losartan, irbesartan, telmisartan and valsartan.[47,48] Twenty four hours after administration, the dose required to induce a 2-fold rightward shift in the angiotensin II dose-response curve was candesartan cilexetil 6mg, telmisartan 54mg, irbesartan 123mg and valsartan 93.5mg.[47] These doses are within the therapeutic dose range for these drugs. In another study, administration of a single dose of candesartan cilexetil 32mg (a dosage approved only in the US) or losartan 150mg (supratherapeutic dose of losartan) induced similar angiotensin II inhibiting activity (reported as blockade of AT_1 receptors), although the inhibitory effect of candesartan cilexetil appeared to be of longer duration.[49] In this study, the extent of receptor blockade achieved by candesartan cilexetil 32mg was 79, 72 and 72% (6, 12 and 24 hours after administration, respectively) compared with 73, 65 and 62% by losartan 150mg. Losartan 50mg induced receptor blockade of 40, 33 and 18%, respectively.[49]

Similar angiotensin II inhibiting activity *in vivo* was reported after administration of single (1 day) or multiple (8 days) doses of candesartan cilexetil 8mg or irbesartan 150mg to healthy volunteers.[46] Data from *ex vivo* experiments in healthy volunteers seem to indicate that irbesartan 150mg induced greater AT_1 receptor blockade than candesartan cilexetil 8mg, but in these studies plasma concentrations of the drugs were not reported.[46,50,51] Because of the tight and long-lasting binding of candesartan to AT_1 receptors its plasma concentration may be low, and hence, its *ex-vivo* activity may be limited.

In vitro co-incubation experiments, in which AT_1 receptor antagonists and angiotensin II were added simultaneously to AT_1 receptor-transfected Chinese Hamster Ovary Cells (CHO-hAT_1), showed that all AT_1 receptor antagonists produced parallel rightward shifts of the dose-response curve.[52,53] However, in pre-incubation experiments (where the antagonist is added before angiotensin II) their effects were surmountable (losartan), partially insurmountable (irbesartan, EXP3174) or almost fully insurmountable (candesartan).[52,53]

Table I. Overview of the pharmacodynamic properties of intravenously administered candesartan or orally administered candesartan cilexetil

Selectively and insurmountably inhibits binding of angiotensin II to angiotensin II subtype I (AT_1) receptors[5,15]
Binds tightly to, and dissociates slowly from, the receptor binding site. Dissociation from the AT_1 receptor is approximately five times slower than that of angiotensin[17]
Has higher affinity for AT_1 receptors than losartan potassium or its active metabolite EXP3174[18,19]
Dose-dependently inhibits the pressor response to exogenous angiotensin II in healthy volunteers; peak effects are reached after 4 to 8 hours[20]
The inhibitory effect of candesartan cilexetil 8mg on the angiotensin II-induced pressor response in volunteers was 1.65 times greater than that achieved with losartan potassium 50mg when measured 24 hours after drug administration[21]
Reduces endothelial dysfunction by restoring tonic nitric oxide release and blunting the vasoconstrictive response to endogenous endothelin-1 in patients with hypertension[22]
Suppresses the formation of intimal hyperplasia in animal models of vascular injury[23,24]
Reduces cardiovascular damage after infarct or injury in animal models of myocardial infarction or intima hyperplasia[25,26]
Increases plasma renin activity and plasma angiotensin II concentrations but not aldosterone concentrations in volunteers and patients with hypertension[27]
Prevents and/or regresses left ventricular hypertrophy in hypertensive patients and animal models[28-33]
Significantly reduces mean arterial pressure and systolic and diastolic blood pressure (BP) without affecting cardiac output, stroke volume or heart rate[20,28,34,35]
Appears to preserve or improve renal function in patients with hypertension and reduces albuminuria in those with coexisting type 2 diabetes mellitus and microalbuminuria[36,37]
Reduces the incidence of stroke in stroke-prone spontaneously hypertensive rats treated from 22 to 32 weeks of age[32]
Appears to maintain cerebral blood flow despite reducing systemic BP in patients with hypertension[5]
Has no effects on blood glucose and lipid metabolism in patients with essential hypertension or coexisting type 2 diabetes mellitus. Limited evidence suggests that candesartan cilexetil improves insulin sensitivity in patients with hypertension[5,38,39]
Limited evidence suggests that candesartan cilexetil increases plasminogen activator inhibitor type 1 concentrations *in vivo*.[40] Data from animal and human models do not support this finding[41,42]

These differences are not related to irreversible binding since all AT_1 receptor antagonists so far tested dissociate from their receptors, albeit at different rates. In CHO-hAT_1 cells, the half-life (t) of the antagonist-receptor complexes was estimated to be 7 minutes for irbesartan, 30 minutes for EXP3174 and 120 minutes for candesartan.[54,55] It has been suggested that candesartan slow dissociation from and rebinding to AT_1 receptors may explain its long-lasting effect in clinical settings (see section 4.3).[56] Compared with placebo or losartan recipients, significant reductions of SBP/DBP 48 hours post-dose have been observed among patients receiving candesartan cilexetil 16mg daily, despite undetectable plasma concentrations of candesartan.[57,58]

2.1.2 Endothelial and Vascular Effects

Patients with hypertension show reduced basal nitric oxide (NO) release, impaired agonist-evoked endothelium-dependent vasodilation and increased endothelin-1 (ET-1). This impairment of endothelial function, probably because of increased angiotensin II activity and/or production, is believed to induce vascular dysfunction and structural changes in the vessels.[22] Candesartan cilexetil improved tonic NO release and reduced the vasoconstrictive effect of endogenous ET-1 in 15 patients with hypertension.[22]

In patients with hypertension, candesartan cilexetil 8 or 16 mg/day reduced plasma ET-1 concentrations from baseline (2.49 ± 1.32 ng/L) after 2 (1.61 ± 0.88 ng/L, $p < 0.05$) and 12 months (0.72 ± 0.53 ng/L) of treatment.[22] Moreover, candesartan cilexetil enhanced vasoconstriction to intra-arterial N^G-monomethyl-L-arginine, a NO synthase antagonist, after 2 and 12 months of treatment (maximum forearm blood flow reduced from baseline by 37%, $p < 0.05$ and 42%, $p < 0.001$, respectively).[22]

2.1.3 End-Organ and Haemodynamic Effects

Treatment of 18 Japanese patients with mild to moderate hypertension with candesartan cilexetil 2 to 12mg once daily for up to 24 weeks reduced left ventricular (LV) mass by up to 9.3%.[5] Moreover,

data from two studies, one of which is presented as an abstract, showed a beneficial effect of candesartan cilexetil treatment on the diastolic function of patients with mild to moderate hypertension.[29,30] Compared with baseline, candesartan cilexetil 16mg once daily for 24 weeks (n = 35) reduced LV hypertrophy (4.4 g/m^2, $p < 0.05$) and forearm vascular resistance at rest and after ischaemia (14.8 and 1.3 units, respectively, $p < 0.01$). Improvement in mean diastolic time (54.2 msec, $p < 0.05$) and peak velocity filling (6.3 cm/sec, $p < 0.05$) were also reported.[30] Similarly, long-term candesartan cilexetil 16mg once daily (52 weeks, n = 114), reduced LV mass index (24 g/m^2, $p < 0.05$), deceleration time (22 m/sec, $p < 0.01$) and isovolumetric relaxation time (8.3 m/sec, $p < 0.01$) [all values are mean change from baseline].[29]

2.1.4 Effect on Renal Function

Candesartan cilexetil improves/preserves renal function and reduces proteinuria in hypertensive patients with concomitant type 2 diabetes mellitus and/or renal impairment without affecting urinary sodium, potassium or uric acid excretion.[5,37]

In patients with hypertension, candesartan cilexetil 4 to 8 mg/day for 2 weeks significantly reduced renal vascular resistance (from 1.62 to 1.37 dyn • sec • cm^{-5} • $1.48m^2 \times 10^{-4}$, $p < 0.05$) and filtration fraction (from 0.302 to 0.258, $p < 0.05$) and increased renal plasma flow (from 329 to 367 ml/min/1.48m^2, $p < 0.05$) and renal blood flow (from 552 to 603 ml/min/1.48m^2, $p < 0.05$).[59] Acute administration of candesartan cilexetil 16mg (single dose) to hypertensive patients induced significant increases of glomerular filtration rate, renal plasma flow and blood flow, and a significant reduction of renal vascular resistance.[20] Similarly, in healthy volunteers, candesartan cilexetil 4, 8, 16 and 32mg significantly increased renal plasma flow.[60] However, in hypertensive patients receiving candesartan cilexetil 16 mg/day for 6 weeks or 4 to 8 mg/day for 2 weeks, the glomerular filtration rate was unchanged.[59,61] Also, candesartan cilexetil 4 to 8 mg/day did not have any effect on parameters of renal function in a study of hypertensive Japanese patients after 2 or 24 weeks' treatment.[5]

The CALM (Candesartan And Lisinopril Microalbuminuria) study[37] (n = 199) indicated that candesartan cilexetil 16mg once a day in hypertensive patients with type 2 diabetes mellitus reduced the urinary albumin to creatinine ratio from baseline by 15 to 42% ($p < 0.001$) and 0 to 43% ($p = 0.05$) after 12 or 24 weeks of treatment, respectively.[37] A recent study (n = 17) of hypertensive patients with diabetic nephropathy, reported mean reductions from baseline in albuminuria (25%, $p < 0.05$) and fractional clearance of albumin (35%, $p < 0.05$).[62] Compared with placebo, candesartan cilexetil 8 to 16 mg/day for 12 weeks significantly decreased median urinary albumin excretion (from 28.5 to 12.2 mg/12h, $p < 0.05$ *vs* placebo) in 35 hypertensive patients with type 2 diabetes mellitus and microalbuminuria.[36] Reductions from baseline in urinary protein excretion were also reported at all evaluation time points after 3 (0.21 g/24h), 6 (0.29 g/24h) and 9 (0.42 g/24h) months of candesartan cilexetil 8 to 16 mg/day treatment, in seven hypertensive patients with coexisting type 2 diabetes mellitus. However, only the reduction observed after 3 months of treatment was statistically significant ($p < 0.01$). [63] Among these patients, increases in creatinine clearance were also reported.

2.1.5 Effect on Plasminogen Activator Inhibitor 1

Plasminogen activator inhibitor 1 (PAI-1) is the main inhibitor of the fibrinolytic system. The effect of candesartan cilexetil on the concentrations of PAI-1 during hypertension has not been clearly established. *In vitro* experiments in animal[41] and human[42] models indicated that candesartan cilexetil reduced PAI-1 concentrations. However, these results were not supported by a study in postmenopausal women with mild to moderate hypertension.[40]

In spontaneously hypertensive rats or rats receiving angiotensin II infusion (which increased PAI-1 concentrations), infusion with candesartan cilexetil (25 μg/kg/min) reduced aortic and cardiac PAI-1 expression.[41] Exposure of human ad-

ipocytes to angiotensin II stimulated PAI-1 release (276%) into the culture medium. This increase was abolished by the addition of candesartan cilexetil. Candesartan cilexetil also reduced PAI-1 release (41%) in adipocytes not challenged with angiotensin II.[42] However, data from a randomised, double-blind trial indicated that candesartan cilexetil 8mg for 12 weeks induced significant increases from baseline (33%, $p < 0.05$ *vs* placebo) in the plasma concentrations of PAI-1 in postmenopausal women. In this study, losartan (50mg), valsartan (80mg) and irbesartan (150mg) had no significant effect on PAI-1 concentrations.[40]

2.2 Hydrochlorothiazide

Thiazides vary in their chemistry and pharmacological effect on the kidney. They mainly act within the lumen of the distal nephron, blocking the luminal transmembrane-coupled Na-Cl transport system. The mechanism by which thiazide diuretics reduce BP is not fully understood. It has been proposed that during long-term therapy, thiazides act by reducing total peripheral resistance probably through a direct vascular effect.[64] Indeed, a small vasodilator effect has been observed in the human forearm after acute administration of high doses of hydrochlorothiazide (8, 25 and 75 μg/min/dL),[65] and it has been suggested that hydrochlorothiazide acts by inhibiting vascular smooth cell carbonic anhydrase, which results in a rise of intracellular pH, activation of potassium channels and vasorelaxation.[66] It is important to note, however, that *in vivo* vasodilation was achieved at plasma concentrations of hydrochlorothiazide higher than those reached during long-term oral treatment.[65] An overview of the main pharmacodynamic properties of thiazide and thiazide-like diuretics is presented in table II.[67]

Table II. Overview of the pharmacodynamic properties of thiazide and thiazide-like diuretics[67]

Reduce blood pressure
Inhibit NaCl transport in the distal convoluted tubule
Moderately increase Na^+ and Cl^- excretion
Some thiazide diuretics are weak inhibitors of carbonic anhydrase
Increase excretion of K^+
Short-term administration effects on Ca^{2+} excretion are variable while long-term administration decreases Ca^{2+} excretion
Short-term administration increases excretion of uric acid
May cause mild magnesuria while long-term use may cause magnesium deficiency
Attenuate the ability of the kidney to excrete dilute urine during water diuresis
May cause extracellular volume depletion, hypotension, hypokalaemia, hyponatraemia, hypochloraemia, metabolic alkalosis, hypomagnesaemia, hypercalcaemia and hyperuricaemia
May decrease glucose tolerance and unmask latent diabetes mellitus
May increase plasma concentrations of low density lipoprotein cholesterol, total cholesterol and total triglycerides

2.2.1 Haemodynamic Effects

Hydrochlorothiazide treatment in patients with hypertension induced changes in plasma volume, cardiac output, mean arterial pressure, stroke volume, heart rate and total peripheral resistance.[64,68] Interestingly, responders and nonresponders to treatment exhibited a different effect of hydrochlorothiazide therapy on some of these parameters.

Hydrochlorothiazide 50mg twice daily for 12 or 36 weeks, after a 4-week placebo run-in period, lowered mean arterial pressure in 13 patients with untreated essential hypertension and DBP >100mm Hg.[68] Compared with the mean baseline value (117.2 mm Hg), these reductions were significant throughout the study duration as shown by the values of mean arterial pressure after 1 (110.5 mm Hg, $p < 0.01$), 4 (109.2 mm Hg, $p < 0.001$), 12 (104.8 mm Hg, $p < 0.001$), 24 (104.9 mm Hg, $p < 0.01$) and 36 (101.4 mm Hg, $p < 0.01$) weeks of treatment.[68] Cardiac output was significantly reduced from baseline at weeks 4 (0.5 L/min, $p < 0.05$) and 12 (0.6 L/min, $p < 0.01$), but at weeks 24 and 36 the difference was not statistically significant. A similar pattern of stroke volume reductions was also observed. Additionally, significant changes in total peripheral resistance or heart rate were not observed. However, classification of patients as responders (>10% reduction in mean arterial pressure, $n = 7$) and nonresponders (<10% reduction, $n = 6$) revealed substantial differences

between the two groups in cardiac output, total peripheral resistance and heart rate, in addition to differences in mean arterial pressure. For example, after 12, 24 and 36 weeks, a decrease in cardiac output of ≈13% was present only among nonresponders. Also, a 10% reduction in heart rate was detected among this group at week 36. Significant reductions of total peripheral resistance (≈12 to 20%, $p < 0.05$) were observed among responders, but nonresponders showed increases (10 to 12%) in this parameter after 12, 24 and 36 weeks of treatment.[68]

2.2.2 Effect in Left Ventricular Hypertrophy

Hydrochlorothiazide therapy reduces LV mass and left atrial size in patients with mild to moderate hypertension. This effect seems inferior to that observed after ACE inhibitor treatment and similar to that observed after treatment with calcium antagonists or β-blockers.[69]

In patients with mild to moderate hypertension and LV mass abnormalities, hydrochlorothiazide 25 to 50 mg/day for 6 months significantly reduced mean values of septum thickness (0.3mm, $p = 0.05$), posterior wall thickness (0.4mm, $p < 0.05$), left atrium size (1.8mm, $p < 0.01$), LV diastolic dimension (2.8mm, $p < 0.001$), LV mass (43.4g, $p < 0.001$) and LV mass index (19.8 g/m^2, $p < 0.001$) [all values *vs* baseline]. With the exception of septum and posterior wall thickness values, the changes induced by hydrochlorothiazide treatment were significantly greater than those observed among isradipine (2 to 10mg twice daily) recipients.[70] Reductions in LV mass (adjusted for patient covariates) and left atrial size have also been reported in large (n = 1105), long-term, randomised, double-blind clinical trials after 1 and 2 years of treatment with hydrochlorothiazide 12.5 to 50 mg/day and other active comparators.[71,72] After 1 year of treatment, reductions in adjusted LV mass were greater (66g, $p < 0.001$) among patients with the greater LV mass baseline values (>350g) and after 1 and 2 years, hydrochlorothiazide therapy induced a 2mm ($p < 0.05$) and 4.6mm ($p < 0.01$) reduction in left atrial size.[71,72] Moreover, these studies suggested that hydrochlorothiazide treatment was similar to captopril and atenolol treatment (regarding LV mass reduction)[72], but superior to diltiazem, clonidine, prazosin, captopril and atenolol treatment (regarding reductions in left atrial size).[71] However, in another study, treatment with hydrochlorothiazide 12.5 to 50 mg/day in 50 patients with mild to moderate hypertension for 6 months was not associated with significant reductions of LV thickness or mass.[73]

Some studies, but not others, suggested a worsening of ventricular arrhythmias during treatment with diurectics.[74,75] In 45 African-American patients with untreated hypertension and moderate to severe LV hypertrophy (LV posterior wall thickness ≥14mm), treatment with hydrochlorothiazide 25 to 50mg twice daily for 4 weeks did not increase the rate of premature ventricular contractions, couplets and short ventricular tachycardia. Among these patients, sustained ventricular tachyarrhythmic episodes were not reported at any time during the study. Moreover, the prevalence of frequent or complex arrhythmias remained unchanged.[76]

3. Pharmacokinetic Properties

The pharmacokinetic properties of the candesartan cilexetil/hydrochlorothiazide combination have not been extensively studied in patients or healthy volunteers. Therefore, the pharmacokinetic properties included in section 3 are mainly from studies in patients and/or healthy volunteers receiving candesartan cilexetil or hydrochlorothiazide as monotherapy.

3.1 Candesartan Cilexetil/ Hydrochlorothiazide Combination

A randomised, double-blind, crossover placebo-controlled study in healthy volunteers receiving candesartan cilexetil 12mg and hydrochlorothiazide 25mg investigated the pharmacokinetic drug interactions of candesartan cilextil and hydrochlorothiazide.[77] Coadministration of candesartan cilexetil had no effect on hydrochlorothiazide peak plasma concentration (C_{max}), time of peak concentration (t_{max}) or elimination half-life ($t_{1/2}$), although it induced a slight but significant decrease

in the area under the serum concentration-time curve (AUC) values of hydrochlorothiazide (752 *vs* 877 ng • h/ml, $p < 0.01$).[77] Also, coadministration of hydrochlorothiazide increased the bioavailability of candesartan by ≈20% and C_{max} by 23%, but t_{max}, $t_{½}$ and mean residence time were not affected.[77]

Unpublished data indicated that the fixed combination tablet and the combination of the separate components were bioequivalent.[78] Most least squares estimates of ratio and 90% confidence intervals for AUC and C_{max} were within the acceptance limits for bioequivalence (0.80 to 1.25), with the exception of those for C_{max} of candesartan (1.26 and 1.31, for the separate component and fixed combination, respectively).[78]

3.2 Candesartan Cilexetil

Candesartan is the active compound formed after hydrolysation of the inactive prodrug candesartan cilexetil. The pharmacokinetic properties of candesartan have been determined in healthy volunteers and in patients (normotensive and hypertensive) with renal or hepatic impairment, and have been recently reviewed in *Drugs*.[16]

3.2.1 Absorption and Distribution

Candesartan cilexetil is rapidly and completely hydrolysed to the active compound, candesartan, during absorption from the gastrointestinal tract. C_{max} increased in a dose-related manner and occurred ≈3 to 5 hours after oral administration (single or multiple doses) of candesartan cilexetil 4 to 16mg to healthy volunteers and various patient groups.[79-82] Similar dose-dependency was observed with AUC. Accumulation of candesartan was not observed after repeated administration of the prodrug. In volunteers receiving a single candesartan cilexetil 8mg dose, the average absolute bioavailability of candesartan was 42% of that seen with intravenous administration and was unaffected by food intake.[5,79,81,83]

After a single intravenous 4mg dose in healthy volunteers, the volume of distribution of candesartan was low, approximately 0.13 L/Kg, likely because of the high *in vitro* plasma protein binding of candesartan (99.8%).[79]

3.2.2 Metabolism and Elimination

In healthy volunteers, candesartan is eliminated through the urine (33%) and faeces (67%) mainly unchanged, although a small amount is metabolised to its inactive metabolite, CV 15959, by cytochrome P450 (CYP) enzymes in human liver microsomes.[79]

The total plasma clearance of candesartan in patients with hypertension (who received oral candesartan cilexetil 2, 4, 8 or 16 mg/day for 28 days, n = 185) was determined to be 14.07 L/h.[84] In healthy volunteers who received oral candesartan cilexetil 1 to 8 mg/day for 1 or 8 days, total plasma clearance was 0.25 and 0.20 L/h/kg, respectively.[43] Renal clearance was 0.64 L/h (10.9 ml/min) after a single candesartan cilexetil 8mg dose. The $t_{½}$ ranged from 9 to 13 hours and was dose-independent. Although in patients with hypertension the pharmacokinetic properties of the drug are influenced by age and weight, adjustment of candesartan cilexetil dosage according to these parameters is not required.[84]

3.2.3 Elderly Patients

Compared with values determined among younger subjects (aged 19 to 40 years) receiving the same candesartan cilexetil dose, C_{max} and AUC values were higher by ≈50 and 80%, respectively, among healthy elderly volunteers (aged ≥65 years). Also, $t_{½}$ was slightly longer among elderly volunteers (9 to 12 *vs* ≈9 hours). However, upon repeated daily administration, accumulation of candesartan or CV 15959 was not observed. No gender-related differences in AUC were observed after adjustment for body mass index (kg/m^2).[80]

3.2.4 Renal Impairment

Compared with hypertensive patients with normal kidney function, hypertensive patients with renal impairment exhibited substantial increases in C_{max} and AUC after repeated doses of candesartan cilexetil. These increases were almost 2-fold among those with severe renal impairment (creatinine clearance <1.8 L/h/1.73m^2). A recent study[85]

categorised hypertensive patients by degree of renal function impairment into normal to mildly, moderately or severely impaired (creatinine clearance >3.6, 1.8 to 3.6 and 0.9 to 1.74 L/h/1.73m^2, respectively). After administration of single or multiple (5 days) doses of candesartan cilexetil 8mg, serum concentrations at trough (24 hours after drug administration) were significantly higher in patients with severely impaired renal function ($p < 0.05$).[85] After administration of a single dose, AUC_{24h} was higher among severely and moderately compared with normal to mildly impaired patients (786 and 825 *vs* 392 mg • h/L, respectively, $p < 0.05$) and similar differences were observed after multiple doses. Moreover, $t_{½}$ was significantly higher among severely impaired patients than among normal to mildly impaired patients after single (12 *vs* 6.7 hours, $p < 0.05$) and multiple dose administration (15.7 *vs* 7.1 hours, $p < 0.01$) [see section 6].[85] Similar pharmacokinetic properties were observed among hypertensive patients undergoing haemodialysis and elimination of candesartan by haemodialysis was negligible.[5,86]

3.2.5 Hepatic Impairment

Patients with mild to moderate liver impairment did not show significant changes in candesartan pharmacokinetic properties after single (1 day) or multiple administration (3 to 5 days) of candesartan cilexetil 12 mg/day. Compared with healthy volunteers, patients showed mean increases in C_{max} (13.8 mg/L), AUC_{∞} (198mg • h/L) and $t_{½}$ (2.7 hours), but these changes were not statistically significant.[82] A similar trend was observed after repeated administration of the drug.[5,82,87] Compared with healthy volunteers, patients with moderate to severe liver impairment showed increases of AUC and C_{max} of 78 and 64%, respectively, after receiving a single dose of candesartan cilexetil 16mg.[88] Therefore, it is recommended that the initial dosage of candesartan cilexetil be reduced among patients with severe hepatic impairment (section 6).[89,90]

3.2.6 Potential Drug Interactions

Coadministration of oral candesartan cilexetil 8, 12 or 16 mg/day with nifedipine (30 mg/day), glibenclamide (glyburide; 3.5 mg/day), digoxin (0.25 mg/day), hydrochlorothiazide (25 mg/day), warfarin (individually adjusted dose) and the combined oral contraceptive ethinylestradiol/levonorgestrel did not induce significant changes in the pharmacokinetic properties of these drugs.[77,85] Moreover, since candesartan is poorly metabolised by CYP system enzymes (section 3.2.2), inhibitors and inducers of these enzymes are not likely to interact with candesartan.[91]

3.3 Hydrochlorothiazide

3.3.1 General Pharmacokinetic Properties

Concentrations of hydrochlorothiazide are higher in whole blood than in plasma (1.6 to 1.8-fold). In plasma, C_{max} values of 70 to 490 mg/L are observed within a t_{max} of 1 to 5 hours after oral administration of hydrochlorothiazide 12.5 to 100mg. Plasma concentrations are linearly related to the administered dose. Plasma $t_{½}$ greatly varies through a 24-hour period in the same individual and has been reported to be 6 to 15 hours. Upon administration with food, C_{max} values decreased by 20%, t_{max} increased by 1.6 to 2.9 hours and bioavailability was reduced by 10%. In patients with renal disease, hydrochlorothiazide $t_{½}$ is prolonged and plasma C_{max} is increased. Hydrochlorothiazide binding to serum proteins ranges from 40 to 68%.[92]

Hydrochlorothiazide is not metabolised and is eliminated rapidly by the kidneys (at least 61% of the administered dose is eliminated within 24 hours). After oral administration of hydrochlorothiazide 12.5 to 100mg, 55 to 77% of the dose is eliminated through the urine as the unchanged drug (>95%).

3.3.2 Drug Interactions

Thiazide diuretics may interact with cholestyramine and colestipol resins, reducing hydrochlorothiazide absorption from the intestinal tract by up to 85 and 43%, respectively.

Hydrochlorothiazide may interact with alcohol and other agents including barbiturates, narcotics, antidiabetic drugs and corticosteroids. Hydrochlorothiazide should not be administered with lithium,

Table III. Efficacy of candesartan cilexetil (CC)/hydrochlorothiazide (HCTZ) combination compared with that of placebo (PL) or other antihypertensive agents. Changes in blood pressure in patients with mild to moderate or severe hypertension in multicentre, randomised, double-blind studies.

Reference	No. of patients	Dosage (mg/day) [duration (wk)][a]	Mean baseline SBP/DBP values (mm Hg)	Sitting BP mean reductions (mm Hg)[b] SBP/DBP[c]	Response rate/ controlled patients (%)[d]
Campbell et al.[93]e	164	CC 16/HCTZ 12.5 [8]	153.2/98.2	12.0‡/7.5‡	61.0‡/51.2
	164	CC 16/PL [8]	153.4/97.5	7.5/5.5	47.6/43.9
Koenig et al.[57]e,f	81	CC 16/HCTZ 12.5 [6]	170.7/108.0	32.2§§§/21.1§§§	98§§§/58§§§
	79	LOS 50/HCTZ 12.5 [6]	170.6/107.3	23.8/14.9	79/28
McInnes et al.[95]e	237	CC 8/HCTZ 12.5 [26]	169.2/102.9	16.2/9.8	54.4/45.1
	116	LIS 10/HCTZ 12.5 [26]	163.3/101.8	18.4/10.3	62.1/44.8
Mimran et al.[96]e,g	93	PL	NR/101-102	NR/NR	NR
	91	CC 4/HCTZ 6.25 [12]	NR/101-102	NR/9.3	NR
	95	CC 4 [12]	NR/101-102	NR/4.9	NR
	89	HCTZ 6.25 [12]	NR/101-102	NR/1.1	NR
Oparil et al.[99]h,i	135	CC 8 or 16/HCTZ 12.5 [4]	156.2/105.0	11.3†††/9.1†††	53/32
	74	PL/HCTZ 12.5 [4]	156.5/105.6	4.1/3.1	29/16
Oparil et al.[100]i,j	141	CC 8 or 16/HCTZ 12.5-25 [52]	144.0/96.4	11.8/9.3	43.3/33.3
Öhman et al.[94]e	151	CC 16/HCTZ 12.5 [12]	159.5/98.4	19.4§§/10.4§	68.2§/60.9§
	148	LOS 50/HCTZ 12.5 [12]	160.5/98.5	13.7/7.8	56.8/49.3
Papademetriou et al.[102]i	62	PL	155/101	3.2/3.7	29/23
	63	CC 32/HCTZ 12.5 [8]	153/100	22.1***†††‡‡‡/ 14.5***†††‡	78/73
	72	CC 32 [8]	151/101	8.6*/10.6***	56/47
	70	HCTZ 12.5 [8]	150/99	5.9/6.3	30/29
Philipp et al.[98]i,k	119	PL	NR	4.6/3.6	30/NR
	60	HCTZ 12.5 [8]	NR	8.5/5.6	38/NR
	123	HCTZ 25 [8]	NR	10.3/7.2	42.5/NR
	41	CC 2 [8]	NR	9.6/7.2	42/NR
	45	CC 2/HCTZ 12.5 [8]	NR	12.1/5.4	41.5/NR
	38	CC 2/HCTZ 25 [8]	NR	13.1/7.4*	47*/NR
	60	CC 4 [8]	NR	7.9/5.7	38.5/NR
	56	CC 4/HCTZ 12.5 [8]	NR	19.4/10.1*	57.5**/NR
	64	CC 4/HCTZ 25 [8]	NR	12.9/7.2*	47*/NR
	131	CC 8 [8]	NR	11.4/8.1	45/NR
	61	CC 8/HCTZ 12.5 [8]	NR	20.6/10.2*	52.5**/NR
	122	CC 8/HCTZ 25 [8]	NR	15.6/10.7*	60**/NR
	36	CC 16 [8]	NR	12.6/10.3	70/NR
	39	CC 16/HCTZ 12.5 [8]	NR	23.0/16.6*†††‡	85**/NR
	43	CC 16/HCTZ 25 [8]	NR	21.5/13.1*	70**/NR
Plouin[97]i,l	94	CC 4/HCTZ 12.5 [8]	155/99.5[m]	11.0†/7.0†	47†/NR
	91	CC 8/HCTZ 12.5 [8]	155/99.5[m]	13.4††/7.9††	54†/NR
	49	PL/HCTZ 12.5 [8]	155/99.5[m]	5.4/3.3	33/NR
Ripley et al.[101]i,n	56	CC 8 or 16/HCTZ 12.5 [4]	NR	NR/8.6††	NR
	29	PL/HCTZ 12.5 [4]	NR	NR/1.9	NR

a	All drugs administered once daily.
b	Presented as sitting systolic BP (SBP) and sitting diastolic BP (DBP).
c	Primary efficacy endpoint in all studies.
d	Patients were classified as responders if they showed sitting DBP values <90 mm Hg or reductions in DBP ≥ 10mm Hg. Controlled patients showed sitting DBP values <90 mm Hg.
e	Drugs administered in fixed combination tablets.
f	Included patients with moderate to severe hypertension (DBP >110mm Hg and ≤ 120mm Hg).
g	Data presented in abstract form. Reported reductions in BP relative to PL. Statistical significance data not provided.
h	Included patients with severe systemic hypertension (DBP ≥ 110mm Hg). Only patients who did not respond to HCTZ treatment received CC. After 1 week of CC therapy the dose was doubled in nonresponders (DBP ≥ 90mm Hg).
i	Drugs administered as separated component tablets.
j	Extension of the the study by Oparil et al.[99] Baseline values from the end of the 4-weeks double-blind study.
k	Response rates estimated from graphically presented data.
l	Only patients who did not respond to HCTZ 12.5 mg/day for 6 weeks received CC as add-on therapy.
m	SBP and DBP mean values calculated from a graph.
n	Data presented for a subset of Black patients, who did not respond to HCTZ treatment, included in Oparil et al.[99]

CC = candesartan cilexetil; **HCTZ** = hydrochlorothiazide; **LIS** = lisinopril; **LOS** = losartan; **NR** = not reported; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* PL; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ *vs* HCTZ monotherapy; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ *vs* CC monotherapy; § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ *vs* LOS/HCTZ or LIS/HCTZ combination.

since it may cause lithium toxicity (see section 6).[89]

4. Therapeutic Use

The therapeutic efficacy of candesartan cilexetil/hydrochlorothiazide combination therapy has been evaluated in a number of randomised, double-blind, multicentre studies (n = 160 to 1038) of up to 52 weeks' duration (table III). In these and other studies, the candesartan cilexetil/hydrochlorothiazide combination was administered, once daily, as a fixed combination tablet[57,93-96] or as separate tablets of the drugs.[97-103] In general, clinical trials included male and female patients with mild to moderate hypertension (sitting DBP 90 to 115mm Hg), although some studies included patients with severe hypertension (DBP ≥ 110mm Hg).[57,99] As many trials included patients previously receiving antihypertensive treatment[93,95] , most studies were preceded by a placebo run-in period of 2 to 4 weeks. Only one study allowed the use of other concurrent antihypertensive drugs.[57] In this clinical trial, candesartan cilexetil/hydrochlorothiazide combination (fixed combination tablet) was added to any pre-existing antihypertensive therapy, which remained unchanged throughout the study.

In all studies, the primary efficacy endpoint was mean reduction from baseline in trough (24 hours after administration) sitting DBP values, but reductions in trough sitting SBP[57,93-95,97,102] and standing DBP and SBP were also reported.[95] Additionally, at treatment endpoint, patients were classified as responders (trough sitting DBP values <90mm Hg or reductions of ≥10mm Hg) or as controlled patients (trough sitting DBP values <90mm Hg). In two studies, patients with mild to moderate[97] or severe hypertension,[99] unresponsive to HCTZ 12.5 mg/day (DBP ≥90mm Hg or >95mm Hg, respectively), received add-on candesartan cilexetil for 8 or 4 weeks. One study reported long-term treatment (52 weeks) with add-on candesartan cilexetil 8 or 16 mg/day in patients unresponsive to HCTZ 12.5 mg/day.[100] Monitoring of 24-hour ambulatory BP was rarely reported.[103]

4.1 Dose-Finding Study

Data from an 8-week, double-blind, randomised, placebo-controlled, multicentre study (n = 1038) indicated that combinations of can-

desartan cilexetil (4, 8 or 16mg) plus hydrochlorothiazide (12.5 or 25mg) are effective in the treatment of patients with mild to moderate hypertension and induce greater reductions of BP than equivalent monotherapy with either drug.[98]

The greatest reduction from baseline in mean sitting DBP (16.6mm Hg) was recorded with candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg combination treatment (table III), which was significantly greater than the reductions obtained with candesartan cilexetil (10.3mm Hg) or hydrochlorothiazide (5.6mm Hg) monotherapy, at the same dosages ($p < 0.01$, both comparisons) [figure 2]. Compared with placebo, all drug combinations tested induced significant reductions ($p < 0.05$) in the mean values of sitting DBP (ranging from 7.2 to 16.6mm Hg), with the exception of candesartan cilexetil 2mg/hydrochlorothiazide 12.5mg (figure 2).

Substantial reductions in mean sitting SBP were also reported (figure 2). As for DBP values, administration of candesartan cilexetil 16 mg/hydrochlorothiazide 12.5mg for 8 weeks induced the greatest reduction of sitting SBP (23.0mm Hg) and appeared the most effective combination treatment (table III). However, the antihypertensive effect of the candesartan cilexetil 32 mg/hydrochlorothiazide 12.5mg combination was not evaluated in this European study. Overall, for the combination treatment, reductions in sitting SBP ranged from 12.1 to 23.0mm Hg compared with 4.6mm Hg among patients receiving placebo. Statistical data for changes in sitting SBP were not provided in this study (figure 2).[98]

The proportion of patients responding to treatment also indicated superiority of the combination treatment (table III).[98] Response rates were significantly higher among patients receiving candesartan cilexetil 4, 8 or 16mg plus hydrochlorothiazide 12.5 or 25mg than among placebo recipients (47 to 85% *vs* 30%, $p < 0.01$; except candesartan cilexetil 4mg/hydrochlorothiazide 25mg, $p < 0.05$). Again, candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg appeared the most efficacious treatment since a greater proportion of patients in this group responded to therapy (85 *vs* 30%, $p < 0.01$ *vs* placebo). Compared with those of either monotherapy alone, response rates seemed greater during combination therapy (38 to 70 *vs* 47 to 85%), but statistical data on direct com-

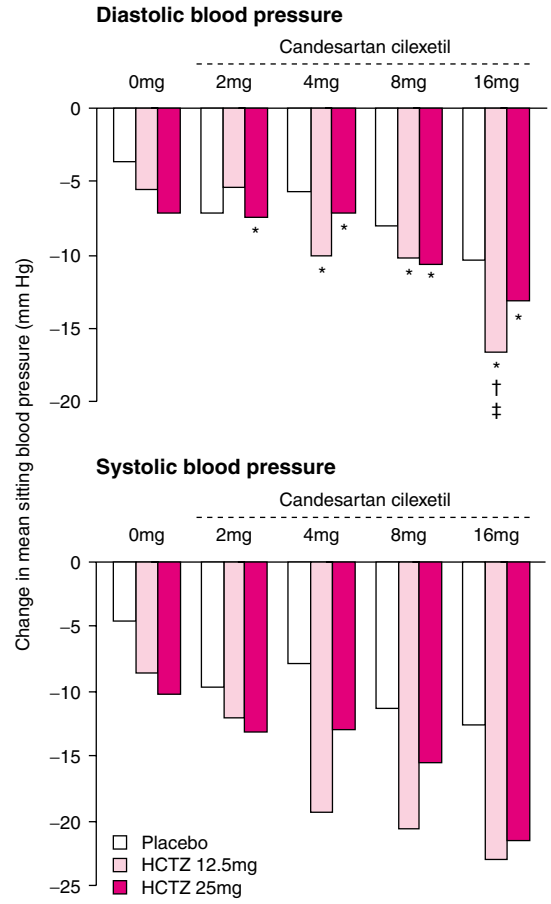


Fig. 2. Main results from an 8-week, randomised, double-blind dose-finding study of patients with mild to moderate hypertension (n = 1038). [98] Following a 2-week washout period and/or a 4-week placebo run-in period, patients were administered placebo or different doses of candesartan cilexetil (CC) and/or hydrochlorothiazide (HCTZ, a fixed combination tablet was not used). Differences from baseline in trough sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) were determined after 8 weeks of treatment. Statistical data for changes in sitting SBP were not provided. * $p < 0.05$ *vs* placebo, † $p < 0.01$ *vs* HCTZ monotherapy, ‡ $p < 0.01$ *vs* CC monotherapy (see table III).

parisons between these treatment groups were not provided.

4.2 Comparisons with Monotherapy

4.2.1 Comparisons with Candesartan Cilexetil or Hydrochlorothiazide

The greater BP lowering effect of candesartan cilexetil/hydrochlorothiazide treatment over candesartan cilexetil or hydrochlorothiazide monotherapy was further demonstrated in clinical trials (table III).

An 8-week, randomised, double-blind, placebo-controlled, multicentre study[93] (n = 328) reported that candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg lowered trough sitting DBP and SBP significantly more than candesartan cilexetil 16mg/placebo, in patients with mild to moderate hypertension who did not respond to candesartan cilexetil 16mg (table III). Reductions from baseline in adjusted mean sitting DBP among patients receiving candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg or candesartan cilexetil 16mg/placebo were 7.5 and 5.5mm Hg, respectively ($p < 0.05$). Reductions in adjusted mean sitting SBP also indicated a greater efficacy of combination therapy over monotherapy (12.0 *vs* 7.5mm Hg, $p < 0.05$). A higher proportion of patients ($p < 0.05$) from the candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg group responded to treatment (61.0%, 95% CI 53.5 to 68.4) than among candesartan cilexetil 16mg/placebo recipients (47.6%, 95% CI 39.9 to 55.2). However, no significant difference was reported between the two treatment groups (51.2 *vs* 43.9%) regarding the proportion of patients in whom BP was controlled (<90mm Hg).[93]

Greater efficacy of the combination therapy over monotherapy was also suggested in three clinical trials, two of which were published as abstracts,[96,102,103] and included patients with mild to moderate hypertension (table III). One double-blind, placebo-controlled, multicentre study (n = 267) evaluated the efficacy of a higher dose of candesartan cilexetil (32mg) in combination with hydrochlorothiazide 12.5mg or as monotherapy.[102] At treatment endpoint (week 8), patients receiving candesartan cilexetil 32mg/hydrochlorothiazide 12.5mg (n = 63) showed greater reductions from baseline in trough mean sitting DBP (14.5 *vs* 10.6mm Hg, $p < 0.05$) and SBP (22.1 *vs* 8.6mm Hg, $p < 0.05$), than those receiving candesartan cilexetil 32mg (n = 72). Additionally, 78% (combination therapy), 56% (candesartan cilexetil) and 30% (hydrochlorothiazide) of patients responded to treatment, although statistical significance was not reported.[102] Moreover, patients receiving low doses of combination therapy (candesartan cilexetil 4mg/hydrochlorothiazide 6.25mg, n = 91) showed added reduction of adjusted mean sitting DBP of 4.4 mm Hg compared with those receiving candesartan cilexetil 4mg (n = 95) [statistical significance not reported].[96]

Data from a randomised, double-blind, placebo-controlled[103] 24-hour ambulatory DBP analysis of patients with mild to moderate hypertension suggested superior efficacy of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg (n = 45) over hydrochlorothiazide 12.5mg monotherapy (n = 41, $p < 0.05$), after 12 weeks of treatment. In this study, 24-hour ambulatory SBP analysis also indicated superior antihypertensive effect of the combination treatment over either drug monotherapy ($p < 0.05$).

4.2.2 In Patients Unresponsive to Hydrochlorothiazide

Data from two randomised, double-blind, placebo-controlled, multicentre studies indicated that combinations of candesartan cilexetil 4, 8 or 16mg/hydrochlorothiazide 12.5mg were significantly more efficacious than placebo in the treatment of patients with mild to severe hypertension who failed to respond to treatment with hydrochlorothiazide 12.5 mg/day for 1 week or more (table III).[97,99]

Patients (n = 234) with mild to moderate hypertension, who did not respond to a 6-week course of hydrochlorothiazide 12.5 mg/day (i.e DBP ≥90mm Hg), received candesartan cilexetil 4 or 8mg or placebo as add-on therapy for 8 weeks. At treatment endpoint, reduction in mean sitting DBP was

greater among patients receiving candesartan cilexetil 4mg plus hydrochlorothiazide 12.5mg (7.0mm Hg, n = 94) or candesartan cilexetil 8mg plus hydrochlorothiazide 12.5mg (7.9mm Hg, n = 91) than among placebo plus hydrochlorothiazide 12.5mg recipients (3.3mm Hg, n = 49; $p < 0.05$ and $p < 0.01$, respectively). Differences in the reduction of sitting SBP between the treatment groups were also significant. Patients receiving candesartan cilexetil 4 or 8mg plus hydrochlorothiazide 12.5mg showed reductions in sitting SBP of 11.0 and 13.4mm Hg compared with only 5.4mm Hg among patients receiving placebo plus hydrochlorothiazide 12.5mg ($p < 0.05$ and $p < 0.01$, respectively). Overall, a greater proportion of responders was observed among patients who received add-on candesartan cilexetil 4 or 8mg than placebo add-on (47 and 54% *vs* 33%, $p < 0.05$).[97]

Add-on candesartan cilexetil 8 or 16mg (n = 135, 84% of patients titrated up to 16mg) for a further 4 weeks was also more efficacious than add-on placebo (n = 74), in patients with severe hypertension (i.e DBP ≥110mm Hg) who did not respond to 1 week of hydrochlorothiazide 12.5mg/day (table III). Primary efficacy endpoint in this study was the mean change in DBP between randomisation point (after 1 week of HCTZ treatment) and endpoint (week 4). At endpoint, mean sitting SBP/DBP was reduced by 11.3/9.1mm Hg in the candesartan cilexetil 8 or 16mg plus hydrochlorothiazide 12.5mg group, compared with 4.1/3.1mm Hg in the placebo add-on group ($p < 0.001$, both comparisons).[99] Additionally, in the candesartan cilexetil plus hydrochlorothiazide group, 53 and 32% of patients were responders or had controlled hypertension, respectively, compared with 29 and 16% of those receiving placebo plus hydrochlorothiazide (statistical significance not reported). Similar differences in reduction of standing SBP/DBP were observed between the two treatment groups.[99] Interestingly, among those receiving candesartan cilexetil plus hydrochlorothiazide, reductions in mean sitting SBP/DBP were greater in patients with higher baseline values of DBP (figure 3, $p < 0.05$, post-hoc analysis). This effect was not observed in the placebo plus hydrochlorothiazide treatment group. Moreover, in a subgroup of Black patients mean reductions in sitting DBP were significantly higher among patients receiving candesartan cilexetil plus hydrochlorothiazide (n = 56) than among placebo plus hydrochlorothiazide recipients (n = 29) [8.6 *vs* 1.9mm Hg, $p < 0.01$].[99] Previously, it had been suggested that antihypertensive treatment is less effective in Black patients.[104]

4.3 Comparisons with Other Combinations

The efficacy of candesartan cilexetil/hydrochlorothiazide was compared with that of losartan/hydrochlorothiazide and lisinopril/hydrochlorothiazide in clinical trials (table III).[57,94,95] Overall, these studies used single, fixed, submaximal doses of the combinations tested; it is not clear if the tested doses are therapeutically equivalent dosages.

Data from two randomised, double-blind, multicentre studies showed that the fixed combination of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg was more efficacious than losartan 50mg/hydrochlorothiazide 12.5mg after 6[57] and 12[94] weeks of treatment (table III). In patients with moderate to severe hypertension both combinations induced substantial reductions in BP after 6 weeks of treatment. However, at endpoint, 24 hours after administration of the last dose, the mean differences in sitting SBP/DBP between the two treatments were 8.4/6.2mm Hg in favour of patients receiving candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg (n = 81, $p < 0.001$, table III). At treatment endpoint, significant differences in favour of candesartan cilexetil/hydrochlorothiazide were also observed at 48-hour postdose evaluation. (16.5/12.2mm Hg, $p < 0.001$).[57] Data from a study in patients with mild to severe hypertension (n = 299) indicated that after 12 weeks of treatment, mean sitting DBP decreased by 10.4 and 7.8mm Hg ($p < 0.05$) among patients receiving a fixed combination of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg or losartan 50mg/hydrochlorothi-

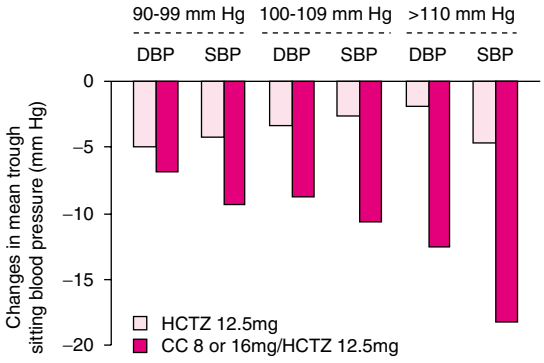


Fig. 3. Blood pressure lowering effect of add-on candesartan cilexetil (CC) treatment in a randomised, double-blind placebo-controlled study of patients with severe systemic hypertension [diastolic BP (DBP) ≥110mm Hg].[99] After a placebo run-in period of up to 2 weeks and 1 week of hydrochlorothiazide (HCTZ) 12.5 mg/day, patients unresponsive to HCTZ (i.e. DBP > 95mm Hg) were randomised to CC 8 or 16 mg/day (n = 135) or placebo (n = 74) for 4 weeks in addition to HCTZ 12.5 mg/day. Changes in mean trough sitting DBP and systolic BP (SBP) are presented per severity of hypertension groups, which were determined by the level of DBP after randomisation. Reprinted with modifications from American Journal of Cardiology, Vol 84, 1999, pp 289-293, Oparil et al: "Effects of candesartan cilexetil in...", with permission from Excerpta Medica Inc.

azide 12.5mg, respectively (table III). Mean differences between the two treatment groups in trough sitting (5.7/2.6mm Hg) and standing (6.0/2.9mm Hg) SBP/DBP reductions favoured the candesartan cilexetil/hydrochlorothiazide combination ($p < 0.05$).[94]

Additionally, response rates in these studies indicated a superior efficacy of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg over losartan 50mg/hydrochlorothiazide 12.5mg. At endpoint (week 6, 24 hours postdose evaluation), a greater proportion of candesartan cilexetil/hydrochlorothiazide recipients were deemed to be responders (98 *vs* 79%, $p < 0.001$) or had controlled BP (58 *vs* 28%, $p < 0.001$) than those receiving losartan/hydrochlorothiazide (table III). Significantly higher response rates were also observed 48 hours after the last dose among those in the candesartan cilexetil/hydrochlorothiazide group.[57] Additionally, in the 12-week study, a greater proportion of responders (68.2 *vs* 56.8%, $p < 0.05$) and controlled patients (60.9 *vs* 49.3%, $p < 0.05$) was reported in the candesartan cilexetil/hydrochlorothiazide treatment group.[94]

It is important to note that in one study,[57] 73% of patients were given the tested combinations as add-on therapy to any other antihypertensive drugs, and in the second study, other antihypertensive drugs were discontinued at randomisation, but a placebo run-in period was not implemented.[94]

Data from a 26-week, randomised, double-blind, multicentre study indicated that candesartan cilexetil 8mg/hydrochlorothiazide 12.5mg (n = 237) was as efficacious as lisinopril 10mg/hydrochlorothiazide 12.5mg (n = 116) in patients with mild to moderate hypertension.[95] The dosages of candesartan cilexetil and lisinopril present in the fixed combination tablets were submaximal. Reductions from baseline in mean sitting SBP/DBP (16.2/9.8 *vs* 18.4/10.3mm Hg) and standing SBP/DBP were reported among patients receiving candesartan cilexetil/hydrochlorothiazide and lisinopril/hydrochlorothiazide, respectively (table III). The adjusted mean differences in SBP and DBP between the two treatment groups were not statistically significant.[95]

5. Tolerability

Candesartan cilexetil/hydrochlorothiazide combination is well tolerated in patients with mild to moderate hypertension. The tolerability profile of this combination has been evaluated in more than 2800 patients with hypertension.[89]

Combined data from five randomised, double-blind, placebo-controlled clinical trials conducted during the preregistration phase in patients with mild to moderate hypertension indicated that adverse events during candesartan cilexetil/hydrochlorothiazide therapy (up to 16mg/25mg once daily) are uncommon and included few of a serious nature (figure 4).[105] Among patients receiving candesartan cilexetil/hydrochlorothiazide (n = 1025) or placebo (n = 526) the incidence of serious adverse events was 1.6 and 2.1%, respectively, while 3.3 and 2.7% of patients discontinued treat-

ment because of adverse events. The most commonly reported adverse events (cumulative 8-week incidence) were headache (3.2 *vs* 5.5% candesartan cilexetil/hydrochlorothiazide and placebo, respectively), back pain (3.0 *vs* 2.4%), dizziness (2.6 *vs* 1.2%) and respiratory infection (2.5 *vs* 1.4%) [figure 4].

In the manufacturer's prescribing information, data from mainly US placebo-controlled trials also indicated good tolerability in patients (n = 1089) receiving various candesartan cilexetil/hydrochlorothiazide combinations (2 to 32mg/6.25 to 25mg, respectively).[89] Adverse events (attributed to treatment or not) reported more frequently with this combination than with placebo recipients were upper respiratory tract infection (3.6 *vs* 3.0%), back pain (3.3 *vs* 2.4%), influenza-like symptoms (2.5 *vs* 1.9%) and dizziness (2.9 *vs* 1.2%). Headache was reported among 2.9 and 5.2% of patients, respectively. Moreover, clinically important changes in laboratory parameters were rarely associated with candesartan cilexetil/hydrochlorothiazide therapy. These included increases in blood urea nitrogen and serum creatinine concentrations, small decreases in haemoglobin (2 g/L), haematocrit (0.4 volume percent) and serum potassium concentrations (0.1 mEq/L) [all laboratory parameters reported as mean changes]. Combined data from placebo-controlled trials indicated that hypokalaemia was reported in 0.4, 1 and 0.2% of patients given candesartan cilexetil/hydrochlorothiazide, hydrochlorothiazide or placebo, respectively. However, among over 2800 patients worldwide receiving this combination, hypokalaemia was observed in at least 0.5% of patients.[89]

Candesartan cilexetil/hydrochlorothiazide, lisinopril/hydrochlorothiazide or losartan/hydrochlorothiazide were all well tolerated among patients receiving these combinations. However, results from a randomised, double-blind, multicentre study[95] showed that, although candesartan cilexetil and lisinopril in combination with low dose hydrochlorothiazide were both well tolerated, the incidence of at least one adverse event (80 *vs* 69%, $p < 0.05$) and cough (23.1 *vs* 4.6%) seemed

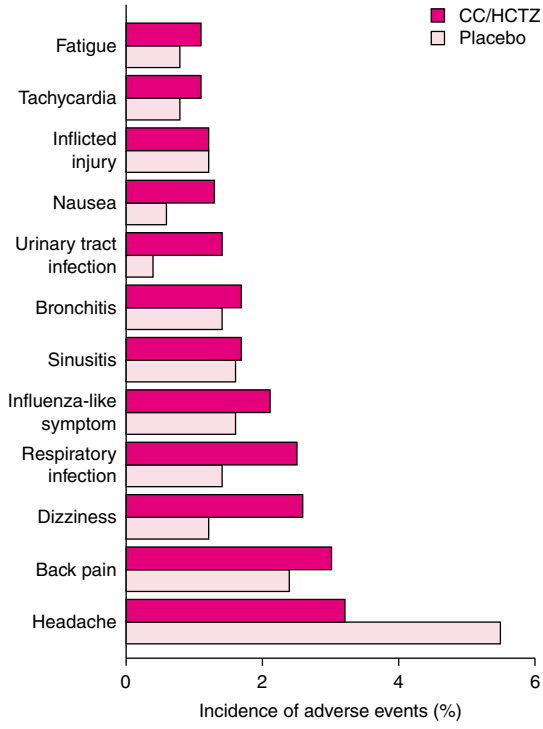


Fig. 4. Adverse event profile of candesartan cilexetil/hydrochlorothiazide in patients with hypertension. Combined data of the cumulative 8-week incidence of adverse events, regardless of attribution to treatment, from five randomised, double-blind, placebo-controlled fixed-dose studies that in patients receiving placebo (n = 526) or candesartan cilexetil/hydrochlorothiazide (CC/HCTZ) [n = 1025; up to 16/25mg once daily].[105]

higher among lisinopril/hydrochlorothiazide recipients. A similar incidence of adverse events was reported among patients receiving candesartan cilexetil/hydrochlorothiazide or losartan/hydrochlorothiazide treatment (see section 4.3 and table III for dosage information).[57,94]

6. Dosage and Administration

The combination candesartan cilexetil/hydrochlorothiazide is indicated for the treatment of patients with hypertension who do not achieve BP control after receiving monotherapy with either drug. In general, a low starting dose of the combination is advised, slowly titrating upward depend-

ing on clinical effect, since this approach minimises the incidence of dose-dependent adverse events. In the US, the recommended daily doses of candesartan cilexetil and hydrochlorothiazide range from 8 to 32mg and 12 to 50mg, respectively, when used as monotherapies.[89] In Europe, the maximum recommended dose of candesartan cilexetil is 16 mg/day.[90] In the US and Europe,[106-109] a combination tablet of candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg is available for patients in whom adequate BP control is not achieved with candesartan cilexetil 16 mg/day, and in the US a candesartan cilexetil 32mg/hydrochlorothiazide 12.5mg combination tablet is recommended in patients whose BP is not controlled by candesartan cilexetil 32 mg/day.[89] In patients in whom BP is not controlled or who are experiencing hypokalaemia with hydrochlorothiazide 25 mg/day, the recommended dosage of candesartan cilexetil/hydrochlorothiazide is 16/12.5 mg/day.[89] Moreover, in some European countries a lower dosage of the combination has been approved (candesartan cilexetil 8mg/hydrochlorothiazide 12.5mg).

Candesartan cilexetil/hydrochlorothiazide combination may be administered to patients with renal impairment if the patient's creatinine clearance is ≥30 L/h. This combination is not recommended in patients with creatinine clearance < 30 ml/min because thiazide diuretics are relatively ineffective. Loop diuretics should be used in patients with this degree of renal dysfunction (see section 3.2.4). Patients with hepatic deficiency should be monitored carefully during administration of this combination, since minor alterations of fluid volume or electrolyte balance by thiazide diuretics may precipitate hepatic coma, particularly in patients with severe liver disease.[89] Patients with moderate to severe liver impairment showed increases of AUC and C_{max} of 78 and 64%, respectively, after receiving a single dose of candesartan cilexetil 16mg (section 3.2.5).[88] Therefore, it is recommended that the initial dosage of candesartan cilexetil be reduced among these patients.[89] Also, patients receiving the combination should be advised to discontinue or avoid potassium supplements.[89]

Candesartan cilexetil/hydrochlorothiazide combination should not be administered to pregnant women. Drugs that act on the RAS can cause fetal and neonatal morbidity and death when administered to pregnant women and, indeed several dozen cases in women taking ACE inhibitors have been reported in the literature.[89] Moreover, candesartan cilexetil (animal data) and hydrochlorothiazide (human data) are excreted in milk, so nursing mothers should be advised to discontinue nursing or discontinue the medication.[89]

The candesartan cilexetil/hydrochlorothiazide combination may be administered with other hypertensive agents and may be administered with or without food.[89]

Thiazide diuretics may interact with other drugs when administered concurrently (section 3.3.2). These interactions may cause orthostatic hypotension (with alcohol, barbiturates or narcotics), dosage adjustment of antidiabetic drugs, hypokalaemia (with corticosteroids and adrenocorticotropic hormone), decreased response to pressor amines and increased response to skeletal muscle relaxants. Moreover, coadministration with NSAIDs may reduce the diuretic, natriuretic and antihypertensive action of thiazide diuretics.[89] Hydrochlorothiazide should not be administered with lithium, since it may cause lithium toxicity.[92]

7. Place of Candesartan Cilexetil plus Hydrochlorothiazide Combination in the Management of Hypertension

Hypertension is an important risk factor for coronary heart disease, stroke, heart failure, renal disease and recurrent cardiovascular events, and reduction of BP is associated with decreased cardiovascular morbidity and mortality.[7,9,10,14,69] More importantly, the correlation between BP and risk of cardiovascular diseases, renal disease and mortality is continuous and is observed also among normotensive individuals. Current recommendations for the treatment of patients with hypertension take into consideration total cardiovascular

risks rather than BP alone and three categories of risk have been established depending on the levels of BP and presence of major risk factors, target organ damage and cardiovascular disease.[8,10]

The World Health Organization (WHO) considers values of SBP/DBP <130/85mm Hg as normal and <120/80mm Hg as optimal BP levels.[10] Current US guidelines[7] recommend SBP/DBP values <140/90mm Hg while UK guidelines[9,110] recommend optimal values of SBP/DBP <140/85mm Hg for most patients or <140/80mm Hg in patients with type 2 diabetes mellitus. Moreover, these guidelines urge improved recognition of the negative effect of high-normal SBP/DBP (130 to 139/85 to 89mm Hg), since optimal BP with respect to cardiovascular risk is <120/80mm Hg.[7]

Substantial reductions in morbidity and mortality associated with hypertension have been achieved in many countries but the majority (>70%) of patients with hypertension remain with inadequate control of their BP.[1] In the UK, only 6% of patients with hypertension had their BP lowered to the recommended levels and in the developing and former socialist countries the incidence of cardiovascular diseases is an ongoing problem.[10] A Canadian health survey indicated that only 59% of individuals with hypertension were aware of their condition and, of those with hypertension, 58% were not receiving any treatment. In France, Germany, Italy and Spain only 13% of hypertensive patients have their BP controlled (SBP/DBP <140/90mm Hg).[111] Moreover, recently in the US, the age-adjusted stroke mortality rates have risen slightly and the rate of decline of coronary heart disease mortality has decreased.[7]

Since detection and treatment of existing hypertension have proven inadequate in many patients, recent guidelines have emphasised the importance of lifestyle modifications to prevent high BP. These modifications include weight reduction, reduction of excessive alcohol consumption, reduction of sodium intake and increased physical activity, and are to be used as definitive treatment or in conjunction with drug therapy.[7,10,110] Complex dietary changes are also recommended and a diet rich in fruits, vegetables and nuts, that includes low-fat dairy products and reduces saturated and total fats has been proven in clinical trials to substantially and significantly reduce BP.[112] Although smoking does not induce increases of BP, smoking cessation is considered by the WHO as the most important lifestyle measure for the prevention of cardiovascular and noncardiovascular diseases and is strongly recommended for all hypertensive patients who smoke.[10] Overall, it is expected that lifestyle changes alone could eliminate the need for antihypertensive drugs or at least they may reduce the number and dosage of hypertensive drugs.[7,113] In practice, however, implementation of lifestyle changes is difficult and is achieved only by highly motivated individuals.

Therefore, it is not surprising that hypertension remains a major problem worldwide and detailed international and national guidelines for its management are frequently updated.[7,9,10] Most patients (>95%) with hypertension are in the medium to high risk category, indicating that many patients will require antihypertensive drugs to control BP.[8] The low compliance levels of patients with hypertension remains a major problem. Fifty to 70% of patients change or discontinue their medication in the first 6 months of therapy, probably because of drug adverse events, cost of treatment and/or poor efficacy, among other reasons.[12] Moreover, control of BP is seldom achieved with monotherapy, therefore, fixed-dose combination products may be particularly useful in achieving target BP levels. Data from randomised, double-blind clinical trials of patients with hypertension, some of whom had type II diabetes mellitus or renal disease, indicated that ≈2.75 to 3.8 different antihypertensive drugs may be required to achieve target BP levels.[2,8]

Data from clinical trials (4 to 52 weeks) indicated that candesartan cilexetil/hydrochlorothiazide combination substantially reduced BP in patients with mild to severe hypertension (section 4). In a dose-finding study, patients receiving candesartan cilexetil 16mg plus hydrochlorothiazide 12.5mg showed the greatest DBP and SBP reduc-

tions and a higher proportion of patients responding to treatment than those receiving placebo or either monotherapy (section 4.1). This combination showed an additive effect, since it was significantly more efficacious than either of the drugs as monotherapy (sections 4.1 and 4.2). The combination is suitable in patients with hypertension who fail to respond to first-line therapy with a diuretic or patients that do not respond to candesartan cilexetil monotherapy. Also, the candesartan cilexetil/hydrochlorothiazide combination is efficacious (table III) and well tolerated during long-term treatment of patients with severe hypertension who do not respond to hydrochlorothiazide monotherapy. Additionally, candesartan cilexetil 16mg/hydrochlorothiazide 12.5mg combination was more efficacious than losartan 50mg/hydrochlorothiazide 12.5mg in patients with mild to severe hypertension, while candesartan cilexetil 8mg/hydrochlorothiazide 12.5mg showed similar antihypertensive action to lisinopril 10mg/hydrochlorothiazide 12.5mg in patients with mild to moderate hypertension (section 4.3). These studies used single fixed submaximal doses of the combinations tested; it is not clear if the tested doses are therapeutically equivalent dosages.

The candesartan cilexetil/hydrochlorothiazide combination is well tolerated (section 5). Clinically important changes in laboratory parameters, including hypokalaemia (≥ 0.5% of patients), were rarely associated with this combination. Moreover, the incidence of adverse events was similar among candesartan cilexetil/hydrochlorothiazide, losartan/hydrochlorothiazide or lisinopril/hydrochlorothiazide recipients, although patients receiving candesartan cilexetil/hydrochlorothiazide seemed less likely to report cough than those receiving lisinopril/hydrochlorothiazide.

The goal of any antihypertensive treatment is to reduce morbidity and mortality due to cardiovascular events. Currently, the WHO guidelines on hypertension recommend the use of diuretics, β-blockers, ACE inhibitors, calcium antagonists, α-blockers and AT_1 receptor antagonists,[10] depending on compelling indications for different patient groups. So far, six AT_1 receptor antagonists have been approved for the treament of hypertension in numerous countries (candesartan cilexetil, losartan, valsartan, irbesartan, eprosartan and telmisartan).[3]

Although BP is only a surrogate biomarker, the capacity of new antihypertensive agents to reduce BP has been sufficient basis for their approval in the treatment of patients with hypertension, even in the absence of outcome data. This approach has been substantially challenged recently by the results of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study.[114,115] In the ALLHAT study (n = 24 335), patients receiving doxazosin (an α-adrenergic receptor blocker) had a statistically significant 25% increase in risk of combined cardiovascular disease events, including a 2-fold increase in congestive heart failure, compared with chlorthalidone (diuretic) recipients. α-Adrenergic receptor blockers have been approved and marketed for the treatment of patients with hypertension for over 20 years. Interestingly, only a 2 to 3 mm Hg difference in SBP reduction between the two treatment groups was observed.[114,116]

Recently, the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program, consisting of three independent randomised, placebo-controlled multicentre studies, has been designed to investigate the effects of candesartan cilexetil on mortality and morbidity among a broad range of patients with symptomatic heart failure (n ≈ 6500).[117] Moreover, in the SCOPE (Study on Cognition and Prognosis in the Elderly) study, the effect of candesartan cilexetil 8 to 16mg once daily on major cardiovascular events is being investigated in patients (70 to 89 years of age) with mild hypertension (n = 4964).[118]

The current guidelines[7,10] for the treatment of patients with hypertension recommend low-dose thiazide diuretics or β-blockers as first-line therapy, since abundant evidence shows their effectiveness in preventing stroke, congestive heart failure, coronary events and all-cause mortality.[13,119,120]

There are also compelling indications for other agents in different clinical conditions (especially comorbid disease), but prescribers should be aware that reduction of long-term cardiovascular morbidity and mortality may not have been conclusively demonstrated for these agents.

In this context, patients treated with the candesartan cilexetil 16mg/hydrochlorithiazide 12.5-mg combination once a day should receive the protective effect against cardiovascular events provided by the thiazide diuretic hydrochlorothiazide while minimising the incidence of adverse events. Since this combination provides 24-hour BP control, its use may improve compliance to treatment and reduce BP variability throughout the day, which has been associated with early morning occurrence of cardiovascular events and development of target organ damage.[10] Also, the renal function of hypertensive patients with type 2 diabetes mellitus and coexisting microalbuminuria receiving treatment with candesartan cilexetil was preserved and urinary albumin excretion was reduced (section 2.1.4).[36,37,62] Moreover, the significant added reduction of BP observed in patients receiving combination therapy will be of benefit to the majority of patients who can not reach their target BP with monotherapy. The questions remain whether this added reduction of BP and/or the use of candesartan cilexetil have a significant effect on the cardiovascular morbidity and mortality of patients with hypertension. A series of ongoing clinical trials, including over 60 000 patients and designed to evaluate the impact of AT_1 receptor antagonists on cardiovascular morbidity and mortality should provide definitive answers to these questions.[3,117,118]

In conclusion, the combination of candesartan cilexetil and hydrochlorothiazide (AT_1 receptor antagonist and thiazide diuretic, respectively) is an effective treatment for patients with hypertension. Data from randomised, double-blind, placebo-controlled clinical trials showed that this combination is significantly more efficacious than either agent alone. Moreover, the combination of these two agents showed an excellent adverse event profile. Current data support the use of this combination as an alternative when monotherapy with either agent is not effective, and there are no compelling or specific indications for other drugs. However, data from large clinical trials, evaluating morbidity and mortality outcomes, are needed to determine the precise role of candesartan cilexetil/hydrochlorothiazide combination in the treatment of patients with hypertension.

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