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EDARBYCLOR®: THE FIRST ANTIHYPERTENSIVE COMBINATION DRUG CONTAINING CHLORTHALIDONE

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Hypertension (HTN) affects approximately 1 in 3 Americans. Despite the availability of multiple drug treatments, HTN remains inadequately controlled with less than half of patients reaching target blood pressure (BP) goals.[1, 2] For uncomplicated HTN, thiazide-like diuretics have been the basis of therapy in most outcome trials, often used in conjunction with other pharmacologic agents.[3] Head-to-head studies demonstrate comparable BP reduction among various drug classes, including angiotensin-converting -enzyme inhibitors (ACEi), calcium channel blockers (CCB), and angiotensin II receptor blockers (ARB). Choice of drug is often based on the potential side effect profile, with ARBs popular due to a tolerability profile similar to placebo.[4-6]

Edarbyclor® (azilsartan/chlorthalidone) is a new antihypertensive developed by Takeda that was approved by the FDA in December 2011. Edarbyclor® is the first fixed-dose therapy in the US to combine an ARB with the thiazide-like diuretic chlorthalidone. This article will review Edarbyclor® (AZL/CHLOR), including its pharmacology and pharmacokinetics, summarize its efficacy and safety data, and describe dosing, cost, and monitoring parameters.

Pharmacology and Pharmacokinetics

Azilsartan medoxomil (AZL-M) is the ARB component of Edarbyclor®. AZL-M is a prodrug that is quickly hydrolyzed in the GI tract to the active moiety azilsartan (AZL), a potent and highly selective ARB. In vivo and in vitro studies have shown AZL binds to the angiotensin 1 (AT1) receptor in a concentration-dependent manner with high affinity compared to other ARBs such as olmesartan, telmisartan, valsartan, and irbesartan. The unique antagonistic profile of AZL, such as the insurmountable antagonism and slow dissociation from the receptor induces long-lasting pharmacologic effects leading to more efficacy in lowering BP in patients with mild to moderate HTN.[7]

After oral administration, peak plasma concentrations are reached within 1.5-3 hours (**Table 1**). The estimated bioavailability is 60% and is unaffected by food. AZL is highly bound to plasma proteins (>99%). AZL is metabolized to two metabolites, MI and MII (majority), that are formed via cytochrome P450 2C9. Due to the metabolites' low affinity for the AT1 receptor, they do not contribute to the pharmacologic activity of AZL. Steady state levels are achieved within 5 days, and no accumulation in plasma occurs with repeated once-daily dosing. The elimination half-life is approximately 12 hours, with about 55% of AZL eliminated in feces, and 42% in urine.[8-11]

After oral administration, chlorthalidone (CHLOR) peak plasma concentrations are reached within 2-6

Inside This Issue:

Table 1 | Azilsartan Pharmacokinetic Properties

Property	Data
Oral bioavailability	60%
Time to peak concentration	1.5-3 hours
Half-life	11 hours
Protein binding	>99%
Metabolism	O-dealkylation, MII (major metabolite) and decarboxylation, MI (minor metabolite)
Excretion	Feces 55%, urine 42%

hours (**Table 2**). The estimated bioavailability is 65% and is unaffected by food. CHLOR is highly bound to red blood cells and 75% bound to plasma proteins. The elimination half-life is approximately 45 hours, with the majority of the drug eliminated unchanged in the urine (50-74%), with some potential biliary excretion.[8-10]

Individually, AZL and CHLOR warrant dosage adjustments for specific populations. The combination product AZL/CHLOR has no recommended dosage adjustments for any specific patient population. However, AZL/CHLOR should be used cautiously in patients with renal impairment, hepatic impairment, hypokalemia, hypotension, hyperuricemia, as well as in the elderly and pregnant patients.

Elevations of creatinine are typically transient, or non-progressive and reversible in patients started on AZL. In patients with mild to moderate renal impairment (estimated Glomerular Filtration Rate [eGFR] 30 -90 ml/min/1.73m2), the Area Under the Curve (AUC) and the max concentration of AZL (Cmax) are elevated; however no dosage adjustment is necessary.[10-11] CHLOR, like other thiazide diuretics, is considered ineffective when the creatinine clearance is less than 30 ml/min. The safety and efficacy of AZL/CHLOR has not been established in patients with severe renal impairment (eGFR < 30 mL/min) and is contraindicated in patients with anuria.[10-11]

In patients with mild to moderate hepatic impairment, the AUC and Cmax of AZL are elevated; however no dosage adjustment is necessary. CHLOR can cause minor alterations of fluid and electrolyte balance, which may precipitate hepatic coma in the susceptible patient. The safety and efficacy of AZL/CHLOR has not been established in patients with severe hepatic impairment.[10-11]

AZL/CHLOR should be used with caution in patients at risk of hypokalemia, hypotension, and hyperuricemia. CHLOR may cause dose-dependent hypokalemia. Concurrent use of digoxin can exacerbate hypokalemic effects. However, in the combination product AZL attenuates hypokalemia associated with CHLOR. In volume- or salt-depleted patients (e.g. those taking high doses of diuretics), volume depletion should be corrected prior to initiation of AZL/CHLOR. Transient hypotension is not a contraindication to treatment. If BP is transiently low, AZL/CHLOR should not be started until BP is stabilized as initiation can worsen hypotension. CHLOR may precipitate gout in certain patients.

The elderly may be more sensitive to effects of either AZL or CHLOR. Patients older than 75 years may have high serum creatinine levels. However, no dosage adjustment is recommended in the elderly. AZL (pregnancy category D) reduces fetal renal function and increases fetal and neonatal morbidity and death. Thus, AZL/CHLOR should not be used in pregnant patients.[8-11]

Clinical Trials

Azilsartan

Multiple studies evaluated the safety and efficacy of AZL including studies comparing AZL with ACEi, CCBs, and diuretics (**Table 3**).

In a randomized, double-blind, multicenter, placebo- and active-controlled trial, White et al. evaluated the safety and efficacy of AZL (40 or 80 mg) compared with placebo, olmesartan (OLM), and valsartan (VAL) in Stage 1 and 2 HTN patients.[12] Eligible men and women at least 18 years of age with HTN were included if their clinic systolic BP (SBP) was ≥150 mm Hg and ≤180 mm Hg and if their 24-hour mean SBP was ≥130 mm Hg and ≤170 mm Hg. A total of 1291 patients from 141 centers in the US and South and Central America were recruited and randomly assigned to placebo, 20 or 40 mg of AZL, 160 mg of VAL, or 20 mg of OLM, all given once daily for 2 weeks. At the end of 2 weeks, patients were force-titrated to 40 or 80 mg of AZL, 320 mg of VAL, 40 mg of OLM, or continuation of placebo once daily for an additional 4 weeks. The primary efficacy end point for assessing efficacy was the

Table 2 | Chlorthalidone Pharmacokinetic Properties

Property	Data
Oral bioavailability	65%
Time to peak concentration	2-6 hours
Half-life	45 hours
Protein binding	75%
Metabolism	Majority excreted unchanged by kidneys
Excretion	Urine 50-74%

Table 3 | Summary of Azilsartan Studies

Study	Patients	Design	Outcomes	Interventions	Results
Bakris, et al (2011)[13]	Clinic SBP 150-180 mmHg & 24-hr mean SBP 130-170 mmHg	N = 1275 R, DB, PG	Change in 24-hr mean SBP by ABPM from baseline	Dosing: AZL 20, 40, 80mg qd vs OLM 40mg qd vs PC Duration: 6 wks	AZL 80mg improved mean SBP vs OLM (p = 0.038); AZL 40mg was noninferior
Sica, et al (2011)[14]	Clinic SBP 150-180 mmHg & 24-hr mean SBP 130-170 mmHg	N = 984 R, DB, PG	Change in 24-hr mean SBP by ABPM from baseline	Dosing: AZL 40, 80mg qd vs VAL 320mg qd Duration: 24 wks	AZL 40mg and 80mg improved mean SBP more than VAL (p<0.0001 for both)
White, et al (2011)[12]	Clinic SBP 150-180 mmHg & 24-hr mean SBP 130-170 mmHg	N = 1291 R, DB, PG	Change in 24-hr mean SBP by ABPM from baseline	Dosing: AZL 40, 80 mg qd vs OLM 40 mg qd vs VAL 320mg qd vs PC Duration: 6 wks	AZL 80mg improved mean SBP more than OLM and VAL (p = 0.009 for both); AZL 40mg was noninferior
Bonner (2010)[10]	Clinic SBP 150-180 mmHg	N = 884 R, DB, PG	Change in clinic trough SBP from baseline	Dosing: AZL 40, 80 mg qd vs RAM 10mg qd Duration: 24 wks	AZL 40mg and 80mg improved clinic SBP more than RAM (p<0.001 for both)
Cushman (2011)[10]	Clinic SBP 160-190mmHg + DBP ≤119mmHg	N = 1085 R, DB, PG	Change in clinic trough SBP from baseline	Dosing: AZL 20, 40 mg qd + CLT 12.5, 25mg qd vs OLM 20, 40mg qd + HCTZ 12.5, 25mg qd Duration: 8 wks	AZL/CLT combos improved clinic SBP more than OLM/HCTZ combos (p-value<0.001 for both)
Weber (2010)[10]	Stage 2 HTN	N = 562 R, DB, PG	Change in 24-hr mean SBP by ABPM from baseline	Dosing: AZL 40, 80 mg qd + AML 5mg qd vs PC + AML 5mg qd Duration: 6 wks	AZL/AML combo improved mean SBP vs PC/AML (p<0.001 for both)

ABPM = ambulatory blood pressure monitoring; AML=amlopdipine; AZL = azilsartan; CLT = chlorthalidone; DB = double blind; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; HTN = hypertension; OLM = olmesartan; PC=placebo; PG = parallel groups; R = randomized; RAM = ramipril; qd= once daily; SBP = systolic blood pressure; VAL = valsartan

change from baseline in the 24-hour mean SBP after 6 weeks of treatment.[12]

All of the active therapies lowered 24-hour mean SBP significantly compared to placebo, and compared to placebo the following mean differences were observed: 320 mg of VAL reduced SBP by -9.5 mmHg (95% CI, -12.6 to -6.3; p<0.001); 40mg OLM reduced SBP by -11.4 mmHg (95% CI, -14.5 to -8.2; p<0.001); AZL 40mg reduced SBP by -14.6 (95% CI, -17.7 to -11.4; p<0.001), and AZL 80mg reduced SBP by -14.9 (95% CI, -18.1 to -11.8; p<0.001). When evaluating the ambulatory BP monitoring, AZL 80mg had lower SBP readings at weeks 2, 4, and 6 weeks compared to VAL or OLM, suggesting greater 24-hour BP control. White et al. concluded that AZL 80mg showed superior efficacy to the other treatment options and AZL-40mg was noninferior.[12]

In a randomized, multicenter, parallel group, double-blind, placebo-controlled study Bakris et al. evaluated the safety and efficacy of AZL compared with placebo and OLM in patients with primary HTN.[13] The eligibility criteria, primary endpoint, and study duration were the same as those used in the study by White et al.[12] A total of 1275 patients were stratified by race and randomly assigned to receive AZL at a dose of 20 mg, 40 mg, or 80 mg (n=851), 40 mg OLM (n=282), or placebo (n=142).[13]

The treatment difference between AZL 80 mg and OLM 40 mg was -2.1 mm Hg (95% CI, -4.0 to -0.1; p=0.038), and the treatment difference between AZL 40 mg and OLM 40mg was -0.92 mm Hg (95% CI, -2.87 to 1.02; p=0.352). Changes from baseline in 24-hour mean SBP were greatest with 80 mg of AZL. Bakris et al. concluded that AZL 80mg showed superior efficacy to OLM and AZL-40mg was noninferior.[13]

In a randomized, double-blind, parallel-group, multicenter trial Sica et al. evaluated the safety and efficacy of AZL compared with VAL in Stage 1 and 2 HTN patients. The 984 eligible patients (18 years of age or older with primary HTN) were randomly assigned in a 1:1:1 ratio into 3 groups: AZL 20 mg every day force-titrated to 40 mg every day after 2 weeks; AZL 20 mg every day force-titrated to 80 mg every day after 2 weeks; or VAL 80 mg every day force-titrated to 320 mg every day after 2 weeks; treatment was continued for an additional 22 weeks for all groups. The primary efficacy endpoint was the change from baseline in 24-hr mean SBP after 24 weeks of

Table 4 | Summary of Chlorthalidone Trials

Study	Patients	Design	Outcomes	Interventions	Results
ALLHAT (2002)[15]	Stage 1 and 2 HTN with at least 1 additional risk factor for CHD events in 55+ yo	N=24,335 R, DB, PG	1°: fatal CHD or non-fatal MI 2°: all-cause mortality, stroke, combined CHD, combined CVD	Dosing: Step 1 = titration of assigned drug: CLT 12.5mg, 25mg qd; AML 2.5mg. 5mg. 10mg qd; LSN 10mg, 20mg, 40mg qd Step 2 = added on as necessary: ATN 25-100mg qd; RES 0.05-0.2mg qd; CLN 0.1-0.3mg bid Step 3 = added on as necessary: HYD 25-100mg bid Duration: 4-8 yrs	1°: no difference b/w treatments 2°: compared to CLT: AML had higher rate of HF (10.2 vs. 7.7%; RR, 1.38; 95% CI, 1.25–1.52). LSN had higher rates of CVD (33.3 vs. 30.9%; RR, 1.10; 95% CI, 1.05–1.16), stroke (6.3 vs. 5.6%; RR, 1.15; 95% CI, 1.02–1.30), and HF (8.7 vs. 7.7%; RR, 1.19; 95% CI, 1.07–1.31).
SHEP (1985)[18,20]	Isolated systolic HTN (SBP 160+ mmHg/ DBP<90mm Hg) in elderly (60+ yo)	N=4,736 R, DB, PG	1°: nonfatal and fatal (total) stroke 2°: CV and coronary morbidity and mortality, all-cause mortality, QOL measure	Dosing: Step 1 = CLT (dose 1: 12.5mg qd or matching PC; dose 2: 25mg qd) Step 2 = ATN (dose 1: 25 mg qd or matching PC; dose 2: 50mg qd) Duration: 22 yrs	1°: Stepped care w/ CLT improved reduced stroke incidence (p=0.0003); 2°: Rates were lower in active group vs placebo. Coronary event: RR 0.74, 95% CI (0.58-0.95) Major CV events: RR 0.68; 95% CI (0.58-0.79) Deaths from all causes: RR 0.87, 95% CI 0.73-1.05)

AML=amlodipine; ATN=atenolol; CLN-=clonidine; CLT=chlorthalidone; CV=cardiovascular; DB = double blind; HTN=hypertension; HYD=hydralazine; LSN=lisinopril; PC=placebo; PG = parallel groups; qd= once daily; QOL=quality of life; R = randomized; RES=reserpine

treatment.[14]

AZL 40 mg and 80 mg lowered 24-hour mean SBP (-14.9 mm Hg and -15.3 mm Hg, respectively) more than VAL 320 mg (-11.3 mm Hg; p<0.001 for 40-mg and 80-mg comparisons vs. VAL). Clinic SBP reductions were consistent with the ambulatory results (-14.9 mm Hg for AZL 40 mg and -16.9 mm Hg for AZL 80 mg vs. -11.6 mm Hg for VAL; p=0.015 and p<0.001, respectively). The reductions in 24-hour mean and clinic diastolic BPs were also greater with both doses of AZL than with VAL (p<0.001 for all comparisons). Small, reversible changes in serum creatinine occurred more often with AZL than with VAL; otherwise, safety and tolerability parameters were similar among the three groups. Results from ANCOVA analysis found AZL had greater ambulatory and clinic BP-lowering effects than full-dose VAL without any meaningful increase in adverse events.[14]

Chlorthalidone

In a handful of large trials CHLOR has been studied as initial therapy and in comparison to other antihypertensives (**Table 4**).

The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) study was a randomized, double-blind trial that compared a traditional thiazide-like antihypertensive with newer classes of antihypertensives to determine which medications work best.[15] Eligible patients were 55 years or older with HTN and at least 1 other coronary heart disease (CHD) risk factor. A total of 33,357 participants from 623 North American centers were randomly assigned to receive CHLOR, 12.5 to 25 mg daily, or sham-titration (n=15255); amlodipine, 2.5 to 10 mg daily (n=9048); lisinopril, 10 to 40 mg daily (n=9054); or doxazosin 2 to 8 mg daily (n=9061) for planned follow-up of approximately 4 to 8 years. Results from intention-to-treat analysis found none of the three test treatments differed significantly from CHLOR in rates of the primary outcome of major CHD events. CHLOR was superior at preventing cardiovascular disease (CVD) events compared to amlodipine, lisinopril, and doxazosin. Each of the newer drugs had significantly higher rates of one or more forms of CVD, and lisinopril and doxazosin had higher rates of combined CVD. The doxazosin arm was stopped early due to a 25% higher rate of combined CVD and a two-fold higher rate of heart failure compared to the diuretic arm. The ALLHAT findings are consistent in large part with evidence from other clinical trials that indicate thiazide-like diuretics, such as CHLOR, are drugs of choice for initial treatment of HTN in most patients due to their superiority in preventing major forms of CVD, tolerability, mortality benefit, and their low cost.[15-19]

The systolic HTN in the elderly program (SHEP) was a randomized, placebo-controlled, multi-site

Table 5 | Pharmacokinetic and Pharmacodynamic Comparison of Chlorthalidone and HCTZ

Drug	Onset, h	Peak effects, h	Half-life, h	Duration, h	Relative dose, mg
Chlorthalidone	2-3	2-6	40 (single dose) 45-60 (long-term dosing)	24-48 (single dose) 48-72 (long-term dosing)	25
HCTZ	2	4-6	6-9 (single dose) 8-15 (long-term dosing)	12 (single dose) 16-24 (long-term dosing)	50

H: hours; HCTZ: hydrochlorothiazide

study of patients aged 60 years or older with isolated systolic HTN that evaluated the potential of CHLOR to reduce the risk of stroke. Participants were randomized to active drug or placebo and were followed monthly until SBP reached goal or the maximum level of stepped-care treatment was received. All 4,736 participants had quarterly clinic visits for an average of 4.5 years. CHLOR therapy resulted in a statistically significant decrease in CV events of heart failure, fatal or nonfatal strokes, and coronary heart disease.[18]

An additional study evaluated the gain in life expectancy from the patients of the SHEP trial 22 years after the beginning of active CHLOR therapy. The primary outcome measures were CV death and all-cause mortality. At the 22-year follow-up, life expectancy gain was 105 days (95% CI, −39 to 242; p=0.07) for all -cause mortality and 158 days (95% CI, 36-287; p=0.009) for cardiovascular death. Each month of active CHLOR treatment was associated with approximately 1day extension in life expectancy.[20]

CHLOR and HCTZ are often considered interchangeable agents within the class of thiazide or thiazide-like diuretics. Some evidence suggests that clinicians may use one of these two agents as the preferred diuretic for treating HTN.[1, 15-21] However, significant pharmacokinetic and pharmacodynamic differences exist between these diuretics. CHLOR is 1.5 to 2.0 times as potent as HCTZ and has a much longer duration of action (Table 5). Studies have given insight into dose equivalence between chlorthalidone and HCTZ at an approximate 25mg: 50mg (1:2 ratio) when based on expected BP reduction.[19] The ALLHAT and SHEP trials showed a mortality benefit with CHLOR, whereas no study to date has shown a mortality benefit with HCTZ.[15,20] Therefore if the degree of BP reduction and mortality benefit are the most important variable in defining outcomes, data overall seems to favor CHLOR; no studies have directly compared the two agents. Thus it is unknown whether these pharmacokinetic and pharmacodynamic features lead to differences in outcomes.[21] To determine if one agent is clearly superior in HTN management, further head-to-head studies should be conducted.

Adverse Effects & Drug Interactions

In an 8-week factorial design trial, the most common adverse reactions of Edarbyclor-treated patients were dizziness (8.9%) and fatigue (2%). While receiving recommended doses of AZL/CHLOR, 8.3% of patients discontinued treatment due to increased serum creatinine and dizziness.[10] A summary of the adverse effects associated with AZL and CHLOR independently is presented in **Table 6**. The pharmacokinetics of AZL and CHLOR are not altered in the combination product.[10-11] No drug interaction studies have been conducted with AZL/CHLOR, though there have been drug interaction studies with AZL independently (**Table 7**).

Table 6 | Adverse Effects of Azilsartan and Chlorthalidone

	Common (1-10%)	Uncommon (<1%)
Azilsartan	CV: hypotension (2%) CNS: dizziness (9%), fatigue (2%) Renal: increased serum Cr (2%), increased BUN	Syncope
Chlorthalidone	Dermatologic: Photosensitivity Endocrine& metabolic: Hypokalemia Gastrointestinal: Anorexia, epigastric distress	Agranulocytosis, aplastic anemia, cholecystitis, constipation, cutaneous vasculitis, diarrhea, dizziness, glycosuria, headache, hepatic function impairment, hypercalcemia, hyperglycemia, hyperuricemia or gout, hyponatremia, insomnia, leukopenia, muscle cramps or spasm, nausea, necrotizing angiitis, pancreatitis, paresthesia, polyuria, purpura, rash, restlessness, sexual ability decreased, thrombocytopenia, urticaria, vomiting, vasculitis, weakness

Dosing, Administration, & Cost

Edarbyclor® (AZL/CHLOR), is available as a once-daily single tablet in two strengths: 40mg-12.5mg and 40mg-25mg. The initial dose of Edarbyclor® is 40mg-12.5mg. If BP does not reach goal in 2-4 weeks of therapy, the dose may be increased to 40mg-25mg. Doses above 40mg-25mg are not likely to be effective. The cost of a 30-day supply of once-daily Edarbyclor® (either strength) varies from $83.77-$103.85. The mean cost from a discount, chain, or independent pharmacy is $83.77, $94.87, and $103.85 respectively.[22]

Summary

AZL/CHLOR is the only fixed-dose therapy combining an ARB with the thiazide-like diuretic chlorthalidone. It is an effective option in HTN patients requiring drug combinations to reach target BP, and may be especially useful in patients intolerant to an ACEi. As of yet there have been no clinical trials comparing the efficacy of AZL/CHLOR with other currently prescribed combination antihypertensive medications. However, the observed efficacy of the two individual drug components reflects its potential as an effective combination antihypertensive in the US market.

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Table 7 | Studied Drug Interactions of Azilsartan

	Interacting drug	Effect	Recommendation
Azilsartan	Amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, warfarin	No clinically significant DDI	May be used concomitantly
	NSAID	Reversible deterioration of renal function, possibly acute renal failure	Monitor patient periodically

BUN=blood urea nitrogen; DDI=drug-drug interactions; NSAID=non-steroidal anti-inflammatory drug

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Clinical Trial Update

Twice daily exenatide vs. glimepiride in patients failing metformin[1]— Guidelines recommend metformin as first-line therapy for patients diagnosed with Type 2 diabetes mellitus (T2DM) due to it's favorable side effect profile and unequivocal efficacy. However, the choice of add-on therapy in patients not attaining A1c goals with metformin alone is less clear. Addition of a sulfonylurea or basal insulin is considered a well-validated option with addition of a thiazolidinedione, glucagon-like peptide-1 (GLP-1) agonist, or dipeptidyl peptidase IV (DPP-IV) inhibitor representing viable options, albeit less validated.[2]

Gallwitz et al. randomized T2DM patients who had not achieved A1c goals with metformin monotherapy to open-label exenatide twice daily or glimepiride daily to determine if exenatide was non-inferior to glimperide.[1] Patients were aged 18-85 years, had a body mass index (BMI) of 25-40 kg/m^2, and had an A1c between 6.5-9%. Exenatide (n=490) was started at 5 mcg twice daily, 30-60 minutes before meals, and titrated to 10 mcg twice daily after 4 weeks; glimepiride (n=487) was started at 1 mg per day before breakfast and titrated at 4 week intervals to the maximum tolerated dose. Randomization was stratified by baseline A1c with categories for A1c of $\leq$ 7.3%, 7.3-8.2%, and < 8.2%; over 50% of patients had a baseline A1c $\leq$ 7.3% while only approximately 13% had an A1c > 8.2%.

Participants were enrolled at 128 centers in 14 countries, most of which were European. The mean age of participants was 56 years, 54% were male, 92% were white, and the mean duration of T2DM was approximately 5.5 years with about 2 years of metformin treatment prior to enrollment. The mean BMI was 32 kg/m^2 and the mean A1c was 7.5%.

The primary outcome was time to inadequate glycemic control, defined as an A1c > 9% after the first 3 months of treatment or more than 7% at two consecutive visits 3 months apart after the first 6 months of treatment. Exenatide non-inferiority was declared if the 97.5% confidence interval (CI) did not cross 1.25; testing for superiority followed if non-inferiority was met. The mean (standard deviation [SD]) exenatide dose attained was 17.35 (4.07) mcg per day compared to 2.01 (1.02) mg per day of glimepiride; the average treatment time was about 2 years.

The primary outcome was reached in 203 subjects in the exenatide group (41%) compared to 262 (54%) in the glimepiride group (hazard ratio [HR] 0.748) meeting non-inferiority criteria and also superiority criteria (95% CI 0.623-0.899; p=0.002). Significantly more patients achieved an A1c of < 7% (p < 0.001) and 6.5% (p=0.001) with exenatide vs. glimepiride. Bodyweight decreased by an average of 3.32 kg (SD: 5.45 kg) in the exenatide group compared to a 1.15 kg (SD: 4.18) increase in the glimepiride group.

Significantly more cases of hypoglycemia were reported with glimepiride compared to exenatide while significantly more patients discontinued study treatment with exenatide due to adverse effects (AEs) compared to glimepiride (49 vs. 17, respectively; p=0.01); after 6 months discontinuation rates due to AEs were not different between groups. Nausea was the most commonly occurring AE with exenatide occurring in 29% of patients; nasopharyngitis, diarrhea, headache, influenza, and back pain were also reported by > 10% of exenatide patients. The most commonly reported AE in the glimepiride group was nasopharyngitis (18%) followed by back pain (11%) and headache (9%).

Potential limitations include the relatively low dose of glimepiride utilized, large proportion of patients with a baseline A1c < 7.3%, open-label design, and lack of ethnic diversity.

For patients failing metformin monotherapy twice daily exenatide may represent a viable add-on therapy to achieve A1c goals.

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