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Torasemide Prolonged Release

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Contents

Abstract

▲ Torasemide prolonged release (PR), a high-ceiling diuretic, inhibits renal tubular reabsorption of sodium and chloride in the thick ascending limb of the loop of Henle.

▲ Relative to the immediate-release (IR) formulation, the PR formulation of torasemide was associated with similar systemic exposure, but significantly slower rates of absorption and lower fluctuations in plasma concentrations, and provided higher natriuretic efficiency and more constant diuresis.

▲ The antihypertensive efficacy of once-daily torasemide PR 5–10 mg was noninferior to that of once-daily torasemide IR 5–10 mg with regard to the change from baseline in sitting diastolic BP (primary endpoint) in a 12-week, randomized, double-blind trial in patients with mild to moderate hypertension.

▲ Sitting systolic BP (SBP) decreased from baseline to a similar extent in the overall population of the treatment groups at week 12. However, daytime SBP decreased to a significantly greater extent with torasemide PR than IR in a subgroup of patients who underwent ambulatory 24-hour BP monitoring.

▲ Patients receiving torasemide PR were more likely to achieve adequate control of BP at weeks 8 and 12 than those receiving torasemide IR.

▲ The PR formulation of torasemide was well tolerated in the clinical trial, with a tolerability profile that was similar to that with the IR formulation.

Features and properties of torasemide prolonged release (Sutril Neo®)	
Indication	
Treatment of essential hypertension in adults' alone or in combination with other antihypertensives	
Mechanism of action	
High-ceiling loop diuretic	
Dosage and administration	
Initial dose	5 mg
Dose if suitable response is not achieved within 4–6 wk	10 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (after administration of a single dose in healthy volunteers)	
Geometric mean maximum plasma concentration (C_{max}) [ng/mL]	5 mg: 571.7 10 mg: 1056.5
Median time to C_{max} (h)	5 mg: 1.3 10 mg: 1.5
Geometric mean area under the plasma drug concentration-time curve from time zero to infinity (ng • h/mL)	5 mg: 1601 10 mg: 3754
Mean elimination half-life (h)	5 mg: 4 10 mg: 4.4
Most common treatment-emergent adverse events in a clinical trial	
Urinary urgency, headache, palpitations, dizziness, fatigue and nasal bleeding	

Hypertension is one of the most treatable risk factors for cardiovascular disease.[1] Sustained reductions of systolic and diastolic BP (SBP and DBP) have been associated with reductions in the risk of stroke, myocardial infarction, coronary heart disease, cardiovascular death and total mortality.[1-3] The diagnosis and treatment of hypertension must take into account not only reductions in SBP/DBP, but also the total cardiovascular risk.[1,2]

The key goal of treatment is to achieve the maximum reduction in the long-term total risk of cardiovascular disease through the initiation of lifestyle modifications and treatment with antihypertensive drugs.[2] Antihypertensive agents should have efficacy in lowering blood pressure to recommended goals, a rapid onset of efficacy, convenient once-daily administration, a clear dose-response effect and an excellent tolerability profile.[4] Patients often require treatment with more than one drug in order to achieve their target BP.[1,2]

Diuretics are among the many classes of drugs used to treat hypertension.[1,2] Torasemide, the most active member of the novel anilinopyridine sulfonylurea derivatives, is a high-ceiling loop diuretic.[5,6] It has been available for many years worldwide as the original immediate-release (IR) formulation.[5,6] To facilitate more gradual diuresis, a prolonged-release (PR) formulation of the drug (Sutril Neo®) with an improved pharmacokinetic profile has been recently developed. This profile reviews the pharmacological and clinical properties of torasemide PR in treatment of essential hypertension.

Medical literature on the use of torasemide in hypertension was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference list of published articles.

1. Pharmacodynamic Profile

This section provides an overview of the diuretic and natriuretic properties of torasemide based on previous reviews,[5-7] the manufacturer's summary of product characteristics (Spanish prescribing information),[8] and two randomized, single-blind, crossover, bioequivalence studies in 16[9] or 20[10] healthy volunteers aged 20–35 years.[9] The single-dose study compared the pharmacological properties of torasemide PR 5 and 10 mg with those of torasemide IR at the same nominal dose.[10] The other study compared the pharmacological properties of the PR and IR formulations of torasemide once daily for 4 days after administration of the first and repeated doses.[9]

The effects of torasemide IR versus furosemide (frusemide) on myocardial fibrosis in patients with chronic heart failure (CHF) in two recent randomized, open-label, 8-month studies (n = 36[11] and 22[12]) are also briefly reviewed. The results of a phase IV study of the effects of the PR formulation of torasemide compared with those of furosemide on myocardial fibrosis in patients with CHF[13] are awaited with interest.

Diuretic and Natriuretic Effects

- Torasemide, a high-ceiling diuretic, inhibits the sodium/chloride/potassium co-transport pump in the thick ascending limb of the loop of Henle, thereby inhibiting renal tubular reabsorption of sodium and chloride.[5-7] This results in reduced interstitial hypertonicity, decreased reabsorption of water, and, ultimately, a pronounced natriuresis and diuresis.[5,7]
- The diuretic and natriuretic effects of torasemide have been well established in clinical studies of intravenous and oral IR formulations of the drug, as previously reviewed.[5-7] Urinary volume excretion and natriuresis increase linearly with the logarithm of increasing torasemide dose.[5,7]
- Relative to an equipotent diuretic dose of furosemide, torasemide IR produces more prolonged water and electrolyte excretion, but does not increase potassium loss to the same extent.[5]
- The diuresis provided by torasemide does not affect the glomerular filtration rate, effective renal plasma flow or acid : base balance.[6]
- Long-term treatment with torasemide 5 or 10 mg was not generally associated with significant decreases in potassium, calcium or magnesium levels in clinical trials in hypertensive patients.[8] In

426 hypertensive patients receiving torasemide for an average of 11 months, hypomagnesaemia (1.3 mg/dL) was reported in only one patient, but many patients were receiving magnesium supplements.[8]

- Torasemide is associated with small, dose-dependent increases in levels of blood urea nitrogen (BUN), creatinine, uric acid and glucose, which are reversible upon treatment discontinuation.[8] In hypertensive patients receiving torasemide 10 mg/day for 6 weeks, the average increases in BUN, serum creatinine, serum uric acid and serum glucose were 1.8, 0.05, 1.2 and 5.5 mg/dL, respectively.[8] With the exception of serum glucose, which increased by a further 1.8 mg/dL during the following year, values did not change with long-term treatment.[8]

- Although torasemide has been associated with small increases in a number of other laboratory values (e.g. plasma lipids, serum alkaline phosphatase, haemoglobin, haematocrit, and the number of erythrocytes, leukocytes and platelets) in clinical studies in patients with hypertension, these changes were not clinically significant.[8,14]

- Torasemide was not associated with an increase in the incidence of tumours or any mutagenic activity in *in vivo* and *in vitro* studies.[8]

Pharmacodynamic Bioequivalence

- The PR and IR formulations of torasemide did not differ significantly with regard to the total urine volume and amounts of sodium, chloride and potassium in the urine over the total 24-hour collection period in the studies of pharmacodynamic bioequivalence.[9,10]

- Although between-formulation differences in these parameters were not significant for most collection intervals,[9,10] there were some exceptions. In the single-dose study,[10] relative to torasemide IR, torasemide PR was associated with a significantly lower urine volume and amounts of sodium, chloride and potassium in the urine during the first hour after administration, but higher values during the interval of 1.5–3 hours (p-values not reported). In the multiple-dose study, urine volume was lower with the PR than IR formulation during the first hour after administration of repeated doses (455 vs 578 mL; $p = 0.049$).

- In the single-dose study, urine density did not differ between the PR and IR formulations over the individual or 24-hour collection periods, with the exception of the interval of 0–0.5 hours in which urine density was significantly higher with torasemide PR than with torasemide IR (1018 vs 1013 kg/L; $p = 0.019$).[10]

Pharmacodynamic-Pharmacokinetic Analysis

- Torasemide PR was associated with higher natriuretic efficiency and more constant diuresis than the IR formulation, as modelled using a regression analysis of the mean observed natriuretic response versus the mean torasemide excretion rate in the single-dose study.[10] Urinary concentrations of torasemide (determined by the excretion rate of the diuretic at short intervals) are relevant in evaluating its pharmacodynamics, as the effects of loop diuretics are determined by their concentrations in the primary urinary filtrate.[10]

- Diuretic and natriuretic responses were significantly different between the PR and IR formulation during the first 3 hours after administration, but not over the total 24-hour period (p-values not reported).[10] The IR formulation was associated with marked initial diuretic and natriuretic responses, with >50% of total natriuresis being produced within the first 3 hours after administration, whereas the slower delivery of the PR formulation to the site of action led to relatively higher natriuretic efficiency and more constant diuresis.

- The cumulative natriuretic responses over the total 24-hour timeperiod with torasemide PR were similar to that with the IR formulation.[10] There were no significant differences between the torasemide PR and IR formulations in the estimated mean maximum drug-induced response (2.19 vs 2.93 mmol/min) or the torasemide excretion rate producing 50% of the maximum drug-induced response (7.23 vs 9.14 μg/min).[10]

Effects on Myocardial Fibrosis

- In patients with CHF, torasemide apparently has cardiac benefits beyond its diuretic effects.[11,12] The deterioration of cardiac function in patients with CHF of hypertensive origin involves myocardial fibrosis, which results from an increase in the synthesis and deposition of collagen type I fibres.[15-18] Oral torasemide IR 10 or 20 mg/day reversed myocardial fibrosis and reduced collagen type I synthesis in patients with CHF, as evidenced by significant ($p < 0.01$) decreases from baseline in collagen volume fraction (CVF) and serum carboxy-terminal propeptide of procollagen type I (PICP) levels in the two 8-month trials.[11,12]
- Torasemide appears to reduce myocardial fibrosis through its ability to inhibit procollagen type I carboxy-terminal proteinase (PCP), which is the enzyme involved in the myocardial extracellular generation of collagen type I molecules.[12] The index of PCP activation (i.e. the ratio of PCP active form to PCP zymogen) decreased from baseline to a significant ($p < 0.05$) extent in patients with CHF receiving torasemide.
- Importantly, these beneficial effects on the reversal of myocardial fibrosis do not appear to be a class effect of loop diuretics.[11,12] Treatment with oral furosemide 20 or 40 mg/day was not associated with significant changes from baseline in CVF,[11,12] PICP levels[11,12] or PCP activation[12] in these trials.
- Torasemide also had beneficial effects on myocardial function in patients with CHF.[11,12] In both trials,[11,12] a significantly ($p < 0.05$) greater number of patients receiving torasemide than furosemide showed improvement of at least one grade in New York Heart Association functional class. Measures of left ventricular cardiac function (i.e. chamber stiffness,[11] ejection fraction[11,12] and end-diastolic volume[12]) showed nonsignificant trends towards improvement in the torasemide, but not the furosemide, groups.

2. Pharmacokinetic Profile

Data concerning pharmacokinetic properties of the PR formulation of torasemide are primarily derived from the single[10] and multiple-dose[9] pharmacological studies described in section 1. Values presented for mean maximum plasma concentrations (C_{max}) and areas under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_{∞}) and at steady state (AUC_{ss}) are geometric means of log-transformed data; unless otherwise stated, other values are arithmetic means.[9,10] Supplementary data are derived from the prescribing information,[8] other studies[19-21] and reviews.[5-7]

Absorption and Distribution

- Both formulations of torasemide were rapidly absorbed.[9,10] After administration of single[9,10] or repeated[9] doses, torasemide was detected in the plasma 15 minutes after administration in most (9 of 10[10] and 15 of 16[9]) of the volunteers receiving the PR formulation and all volunteers receiving the IR formulation, and remained detectable in the plasma for at least 24 hours in all volunteers after administration of both torasemide PR and IR.[9,10]
- C_{max} values were significantly lower with torasemide PR than with torasemide IR (figure 1a).[9,10] The ratio of C_{max} values for torasemide PR and IR were 0.82 (90% CI 0.68, 0.98) and 0.68 (90% CI 0.68, 0.78) for the 5- and 10-mg doses in the single-dose study,[10] and 0.69 (90% CI 0.67, 0.73) and 0.62 (90% CI 0.55, 0.70) following the first and repeated 10-mg doses in the multiple-dose study.[9]
- However, total systemic exposure to torasemide, as assessed by AUC values, was similar for both formulations (figure 1b).[9,10]
- Based on AUC_{∞} values, the bioavailability of a single 5- or 10-mg dose of torasemide PR relative to that the same nominal doses of the IR formulation was 103% (90% CI 90, 116) and 107% (90% CI 99, 114).[10] In the multiple-dose study, the corresponding values for torasemide PR 10 mg were 107% (90% CI 102, 111) after the first dose, and 102% (90% CI 98, 105) after repeated doses (based on AUC_{∞} and AUC_{ss} values, respectively).[9]
- All of the 90% confidence intervals (CIs) for the bioavailability of torasemide PR relative to torasemide IR were within the accepted equivalence range of 80 to 125.[9,10]

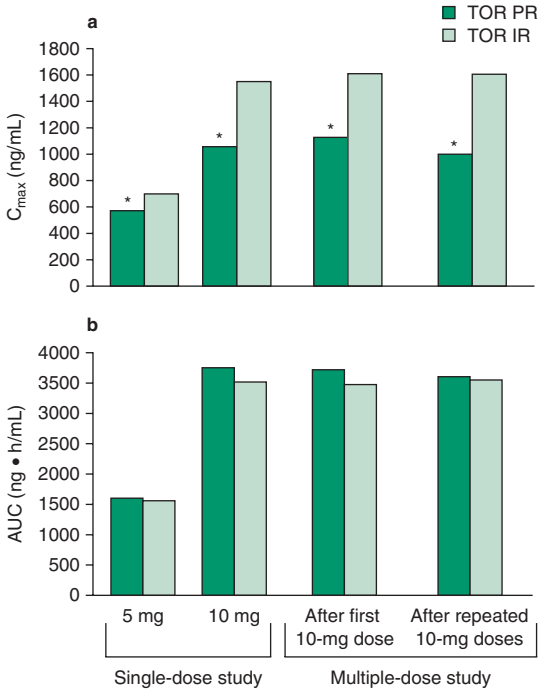

Fig. 1. Pharmacokinetics of oral torasemide prolonged release (TOR PR) vs torasemide immediate release (TOR IR). Geometric means of log-transformed data for (**a**) maximum plasma concentration (C_{max}) and (**b**) area under the plasma concentration-time curve (AUC) after single 5- or 10-mg doses of TOR PR and IR,[10] or after the first or repeated doses of TOR PR or IR 10 mg once daily for 4 d in two randomized, single-blind, crossover studies in 16[9] or 20[10] healthy volunteers. Single-dose AUC values are from time zero to infinity and multiple-dose AUC values are at steady state. * indicates a significant difference vs TOR IR (p-values not reported).

- The time to C_{max} (t_{max}) was significantly longer with torasemide PR than torasemide IR.[9,10] Median t_{max} values for single 5- and 10-mg doses of torasemide PR and IR were 1.3 versus 0.7 hours ($p = 0.03$) and 1.5 versus 0.7 hours ($p = 0.01$).[10] In the multiple-dose study, torasemide PR 10 mg also had significantly ($p \leq 0.003$) longer median t_{max} values than IR formulation after the first or repeated doses (1.5 vs 0.8 and 1.5 vs 0.7 hours).[9]
- After repeated doses, mean minimum plasma concentrations (C_{min}) did not differ significantly between the PR and IR formulations of torasemide 10 mg (5.31 vs 4.29 ng/mL).[9] However, fluctuations in plasma concentrations (percentage of peak-trough fluctuations calculated as C_{max} minus C_{min} divided by the average concentration) were significantly lower with the PR than IR formulation (669% vs 1114%; $p = 0.001$), resulting from the more sustained plasma concentrations shown with torasemide PR.[9]
- Mean residence time (MRT) was also significantly ($p = 0.001$) longer with torasemide PR 10 mg than with torasemide IR 10 mg in the single-dose trial (4.4 vs 3.5 hours),[10] or after the first or repeated doses (4.2 vs 3.5 and 4.3 vs 3.5 hours) in the multiple-dose study.[9] There was no between-formulation difference in the MRT of single-dose torasemide PR 5 mg (4.2 vs 4.0 hours).[10]
- Torasemide is highly bound to plasma protein (>99%).[7] As a result, the volume of distribution (V_d) of the drug (12–15 L[8]) is approximately that of the extracellular fluid volume.[6]
- Although administration of torasemide with food reduced C_{max} by 21% and AUC by 11%, the effect of food on the pharmacokinetics of torasemide is not considered clinically relevant.[8]

Metabolism and Elimination

- In patients with normal renal function, ≈80% of a dose of torasemide undergoes extensive hepatic metabolism[8] (specifically by the cytochrome P450 [CYP] 2C9 isoenzyme).[22] The primary metabolite of torasemide is the biologically inactive carboxylic acid derivative.[7,8,21] Although two of the other metabolites possess some diuretic activity, they are not considered to exert clinically significant diuretic effects as they do not attain sufficient concentrations in the urine.[6,7,21]
- Approximately 20% of a dose of torasemide is excreted in the urine as unchanged drug.[8] Free torasemide has a renal clearance of ≈640 mL/min, which is equal to renal plasma flow.[7] This high renal clearance results from active tubular secretion in the proximal tubule,[7] and appears to involve organic anion transporting polypeptides (OATPs).[20]
- The terminal plasma elimination half-life ($t_{½}$) of torasemide PR was not significantly different from that of torasemide IR.[9,10] In the single-dose study,[10] mean $t_{½}$ values for the PR and IR

formulations of torasemide 5 and 10 mg were 4.1 versus 4.4 and 4.4 vs 4.5 hours. Corresponding values for torasemide 10 mg in the multiple-dose study were 4.1 versus 4.2 hours after first dose and 4.1 hours for both formulations after repeated doses.[9]

- The metabolism and renal clearance of torasemide is affected the presence of certain genetic polymorphisms of the CYP2C9 (*CYP2C9*) and OATP1B1 (*SLCO1B1*) alleles.[19] In a recent study in patients with hypertension or CHF, mean dose-normalized AUC values for torasemide were significantly increased in patients with the *CYP2C9**3 and *SLC01B1*c.521TC alleles.[19]

Special Patient Populations

- The pharmacokinetics of torasemide in healthy elderly individuals are similar to those in younger individuals, although clearance (CL) may be reduced in elderly patients with an age-related decline in renal function.[8] Dosage adjustments are not required in elderly patients.[8]
- Renal CL (CL_R) of torasemide is reduced in patients with renal insufficiency.[8] These patients may require higher dosages of torasemide PR to obtain the desired diuretic effect, as the reduction in CL_R leads to a decrease in the amount of torasemide reaching its urinary site of action and, ultimately, a reduction in overall natriuresis.[8] Plasma CL and $t_{½}$ values are not changed, as metabolic elimination by the liver remains intact.[8]
- In patients with decompensated CHF, total CL of torasemide is ≈50% of that in healthy volunteers.[8] Hepatic CL and CL_R of torasemide are both reduced (probably due to hepatic congestion and reduced renal plasma volume) and overall natriuresis is reduced.[8]
- The V_d, $t_{½}$ and CL_R of torasemide are increased in patients with hepatic cirrhosis relative to values in healthy volunteers, but total clearance is not altered.[8]

Potential Drug Interactions

- Coadministration of torasemide with a variety of other drugs, including spironolactone, β-adrenergic antagonists, calcium channel antagonists, ACE inhibitors, angiotensin II receptor antagonists, cardiac glycosides (e.g. digoxin), organic nitrates, glibenclamide (glyburide), warfarin, phenprocoumon and cimetidine, was not associated with clinically significant effects requiring dosage adjustments in studies in various patient populations or healthy volunteers.[5,6,8,19]
- As torasemide competes for CL_R with lithium and salicylates, concomitant administration of torasemide with lithium or high-dose salicylates may increase the toxicity of these agents, although such interactions have not been studied.[8]
- The diuretic and natriuretic activity of torasemide may be reduced when it is coadministered with probenecid (which blocked the active renal tubular secretion of torasemide in healthy volunteers[23]), indometacin (which partially inhibited the activity of torasemide in volunteers receiving a sodium-restricted diet [50 mEq/day], but not in those receiving a normal sodium diet [150 mEq/day][24]) or colestyramine (which reduced the absorption of oral torasemide in animal studies).[8]
- Although the potential interaction between torasemide and aminoglycoside antibacterials or etacrynic acid has not been studied, concomitant use of these agents with other diuretics has been associated with an increase in ototoxicity, especially in patients with renal insufficiency.[8]

3. Therapeutic Efficacy

The efficacy of once-daily torasemide PR in the treatment of mild to moderate essential hypertension was compared with that of torasemide IR in a 12-week, randomized, double-blind, multicentre, noninferiority trial.[25]

The trial included patients aged 18–75 years with newly diagnosed mild to moderate hypertension (defined as SBP 140–179 mmHg and DBP 90–109 mmHg) or who had inadequate control with, or could not tolerate, their current antihypertensive medication.[25] Among key exclusion criteria were a history of unresponsiveness to diuretic monotherapy or the need to use combination therapy to control BP.[25]

After discontinuation of any previous antihypertensive medication and a 2-week placebo run-in period, patients were randomized to receive either the PR (n = 219) or IR (n = 223) formulation of torasemide 5 mg once daily in the morning.[25] The dosage of torasemide PR or IR could be increased to 10 mg once daily at week 4 or 8 in patients who had not achieved <10% decrease from baseline in DBP; 49.5% and 55.3% of patients in the torasemide PR and IR groups had their dosage increased to 10 mg/day.[25] At week 8, patients whose BP control was inadequate despite receiving once-daily torasemide 10 mg for the previous 4 weeks were withdrawn from the study.

Treatment groups had similar demographic and baseline characteristics at randomization.[25] Across treatment groups, mean values for patient age and weight were 55 years and 78 kg, most (>99%) patients were White, 39% received torasemide because of newly diagnosed hypertension, 52% because of inadequate BP control with previous antihypertensives and 9.7% because of intolerance to previous antihypertensives.

The primary endpoint was the mean decrease from baseline in sitting DBP at the end of the study (week 12); the criterion for noninferiority was predefined as a one-sided 97.5% CI of <2 mmHg for the difference between the PR and IR formulations in this parameter. Secondary endpoints included the mean change from baseline in sitting SBP and the percentage of patients with adequate BP control (defined as SBP <140 mmHg and/or DBP <90 mmHg), as well as mean changes from baseline in various assessments of BP in a subset of 100 patients who underwent ambulatory 24-hour BP monitoring (ABPM) at baseline and week 12.[25] Between-formulation changes in BP and ABPM were assessed using an ANCOVA and repeated measures ANOVA, respectively.[25]

The 12-week trial period was completed by 183 (83.5%) and 197 (88.3%) of patients in the torasemide PR and IR groups (per-protocol [PP] population); 18 (8.2%) and 16 (8.2%) of patients withdrew from the study because of a lack of BP control. Results from the PP population plus those who withdrew because of a lack of response were used to conduct the primary efficacy analysis using last observation carried forward (LOCF) imputation (PP-LOCF; n = 201 and 213 in the torasemide PR and IR groups).[25]

- The mean change from baseline in sitting DBP in torasemide PR recipients was not significantly different from that in torasemide IR recipients at 12 weeks in the PP-LOCF populations (−11.6 mmHg [95% CI −10.6, −12.5] vs −11.3 mmHg [95% CI −10.2, −12.3]; primary endpoint) [figure 2] with both groups showing significant decreases from baseline (p-values not reported).[25]

- The antihypertensive efficacy of torasemide PR was considered to be noninferior to that of torasemide IR; the between-formulation difference in mean change in sitting DBP (−0.61 mmHg; 95% CI −1.91, 0.69) fulfilled the noninferiority criterion (i.e. the one-sided 97.5% CI of in the PP-LOCF population was less than the prespecified margin of 2 mmHg).[25]

- These results were confirmed in a sensitivity analysis carried out in other patient populations.[25] The one-sided 97.5% CI for the between-formulation difference in mean change in sitting DBP was less than 2 mmHg in the PP population (−1.05 mmHg; −2.22, 0.11), in all randomized patients (−0.78 mmHg; −1.99, 0.44), and in all randomized patients using LOCF methodology (−0.29 mmHg; −1.62, 1.03).[25]

- Mean changes from baseline in sitting SBP at 12 weeks did not differ significantly between torasemide PR and IR recipients in the PP-LOCF populations (−17.3 mmHg [95% CI −15.7, −18.2] vs −17.2 mmHg [95% CI −15.7, −18.6]; figure 2), with both treatment groups showing significant changes from baseline (p-values not reported).[25]

- Patients receiving torasemide PR were more likely to achieve adequate control of BP than those receiving torasemide IR.[25] At week 12 in the PP population, adequate BP control was achieved by 25% more patients receiving the PR formulation of torasemide than receiving the IR formulation (63.9% vs 51.3% [p = 0.013]; relative risk 1.25

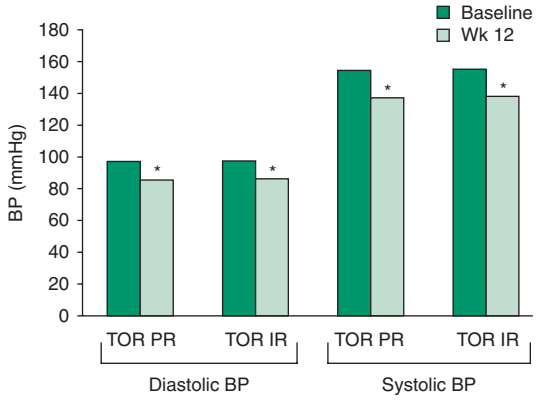

Fig. 2. Antihypertensive efficacy of oral torasemide prolonged release (TOR PR) vs torasemide immediate release (TOR IR) in patients (pts) with mild to moderate essential hypertension. Mean sitting diastolic BP (primary endpoint) and systolic BP values at baseline and wk 12 in pts receiving 5–10 mg of TOR PR (n = 201) or TOR IR (n = 213) once daily in a 12-wk, randomized, double-blind, multicentre, noninferiority trial.[25] Results shown are from the per-protocol population of all pts who completed treatment plus pts who withdrew from treatment at wk 8 because of a lack of response, using last observation carried forward imputation. * indicates a significant difference vs baseline (p-values not reported).

[95% CI 1.05, 1.48]).[25] The between-formulation difference in this parameter was also significant at week 8 (69.4% vs 58.4%; p = 0.025), but not at week 4 (42.1% vs 35.%).[25]

- In the subgroup of patients who underwent ABPM measurements, mean daytime SBP was significantly lower with torasemide PR than with torasemide IR at week 12 (128.4 vs 133.5 mmHg; p = 0.02 [respective baseline values 139.5 and 141.8 mmHg]).[25]
- However, between-formulation differences in all other ABPM parameters (24-hour SBP and DBP, daytime DBP and mean BP [MBP], and night-time SBP, DBP and MBP) were not significant.[25] ABPM values for night-time SBP, DBP and MBP were significantly (p < 0.001) lower than the corresponding daytime values in both the torasemide PR and IR treatment groups.[25]

4. Tolerability

Descriptive tolerability data for torasemide PR are derived from the 12-week trial in patients with mild to moderate hypertension discussed in section 3.[25]

- The tolerability profile of the PR formulation of torasemide was similar to that of the IR formulation.[25] Treatment-emergent adverse events were reported by less than one-third (29.7% and 29.1%) of patients receiving torasemide PR and IR. The majority (>95%) of adverse events were considered to be of mild or moderate intensity.
- The proportion of patients in the clinical trial who discontinued treatment because of adverse events was low in both the torasemide PR and IR treatment groups (1.8% and 2.2%).[25]
- The most frequently reported treatment-emergent adverse events in the clinical trial were headache, palpitations, dizziness, fatigue and nasal bleeding (rate of events in treatment groups not reported).[25] Urinary urgency was reported in 47.0% of patients receiving torasemide PR and 51.2% of patients receiving torasemide IR. No serious drug-related adverse events were reported.[25]
- Treatment with torasemide was not associated with any clinically relevant changes in vital signs, physical examinations, ECG measures or laboratory blood parameters (including potassium and other ion levels, glucose levels and lipid profiles) in the clinical trial.[25]

5. Dosage and Administration

The initial recommended dosage of torasemide PR is 5 mg once daily, which may be increased up to 10 mg once daily if a suitable reduction of BP is not obtained within 4–6 weeks. If a sufficient BP response is not achieved with this dosage, an additional antihypertensive agent should be prescribed.[8] Torasemide PR is administered orally with or without food, and must be swallowed whole.[8]

Local prescribing information should be consulted for further details on the use of torasemide PR in the treatment of essential hypertension.

6. Torasemide Prolonged Release: Current Status

The PR formulation of torasemide is approved as a treatment for essential hypertension in Spain and some Central and South American countries. It may be used as monotherapy or in combination with other antihypertensives.

In bioequivalence studies, systemic exposure to torasemide with the PR formulation was similar to that with the IR formulation, but the PR formulation was associated with a significantly slower rate of absorption and lower fluctuations in plasma concentrations, and provided higher natriuretic efficiency and more constant diuresis. In a well designed trial in patients with mild to moderate hypertension, torasemide PR 5–10 mg once daily was noninferior to torasemide IR 5–10 mg once daily with regard to the primary of changes from baseline in mean DBP. The proportion of patients who achieved adequate BP control was significantly higher with the PR formulation than with the IR formulation at 8 and 12 weeks. Both formulations of torasemide were similarly well tolerated.

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