

Device May Control Refractory Hypertension

BY BRUCE JANCIN

ORLANDO — An innovative implantable device therapy that stimulates baroreceptors safely achieved dramatic long-term blood pressure reduction in patients with refractory hypertension in a phase II study.

On the basis of the highly favorable phase II results, a pivotal phase III clinical trial of the Rheos hypertension sys-

tem is well underway, Dr. Marcos Rothstein said at the annual meeting of the American College of Cardiology.

The Rheos system consists of a pacemaker-like pulse generator that is surgically implanted near the clavicle, baroreceptor activation leads wrapped around each carotid sinus, and an external programmer. Electrical stimulation of the baroreceptors causes vasodilation, natriuresis, diuresis, and reduction in heart

rate, with a resultant dose-dependent decrease in blood pressure, explained Dr. Rothstein, professor of medicine at Washington University in St. Louis.

The phase II study involved 38 American and European patients with stage 2 hypertension. Their mean office cuff blood pressure was 183/105 mm Hg despite an average of 5.1 antihypertensive medications.

After 1 year on the Rheos system,

their systolic and diastolic blood pressures dropped by 25 and 15 mm Hg, respectively, and after 3 years, by 31/21 mm Hg. Mean heart rate declined from 78 bpm at baseline to 71 bpm at 1 year and 73 at 3 years. Meanwhile, participants' total antihypertensive drug dosage dropped by more than one-quarter.

These changes were associated with significant improvement in cardiac structure and function. Mean left ventricular mass decreased from a mean baseline of 132.8 g/m² to 107.8 gm² at 1 year. Left atrial dimension diminished by 2.4 mm from a baseline of 44.1 mm. And mitral wave E and A velocities declined by about 10%, Dr. Rothstein said.

Importantly, 24-hour ambulatory monitoring showed that diurnal variation in blood pressure was maintained.

The complication rate associated with the Rheos system was about 20%. Rough-

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ly three-quarters of the problems were related to the implantation procedure.

More than 17 million Americans have uncontrolled hypertension despite medical treatment. Dr. Rothstein said the Rheos device is aimed at the estimated 1 million or more patients with severe persistent hypertension resistant to three or more drugs and no significant anatomic contraindications. "They have the highest possible risk for early death, strokes, heart attacks, and kidney disease. These patients need an entirely new approach to their treatment," he observed.

Discussant Douglas L. Mann said that the phase II data were "fascinating and compelling."

"I'm particularly impressed with the impact on structural heart disease. Most people would agree that preventing end-organ damage with your therapy is indeed beneficial," said Dr. Mann, professor and chief of cardiovascular medicine at Washington University in St. Louis.

The study was sponsored by CVRx Inc. Dr. Rothstein disclosed having no financial conflicts of interest. ■

TOVIAZ™ (fesoterodine fumarate) extended release tablets

Rx only

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Toviaz is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Bladder Outlet Obstruction: Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Decreased Gastrointestinal Motility: Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

Controlled Narrow-Angle Glaucoma: Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks (see **CONTRAINDICATIONS**).

Reduced Hepatic Function: There are no dosing adjustments for patients with mild or moderate hepatic impairment. Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Myasthenia Gravis: Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

Reduced Renal Function: There are no dosing adjustments for patients with mild or moderate renal insufficiency. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal insufficiency (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Concomitant Administration with CYP3A4 Inhibitors: Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin).

In patients taking weak or moderate CYP3A4 inhibitors (e.g. erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. While this specific interaction potential was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be informed that Toviaz, like other antimuscarinic agents, may produce clinically significant adverse effects related to antimuscarinic pharmacological activity including constipation and urinary retention. Toviaz, like other antimuscarinics, may be associated with blurred vision, therefore, patients should be advised to exercise caution until the drug's effects on the patient have been determined. Heat prostration (due to decreased sweating) can occur when Toviaz, like other antimuscarinic drugs, is used in a hot environment. Patients should also be informed that alcohol may enhance the drowsiness caused by Toviaz, like other anticholinergic agents. Patients should read the patient leaflet entitled "Patient Information TOVIAZ" before starting therapy with Toviaz.

Drug Interactions

Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Also see **PRECAUTIONS, Concomitant Administration with CYP3A4 Inhibitors**.

Drug-Laboratory Test Interactions

Interactions between Toviaz and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11- to 19-fold (females) and 4- to 9-fold (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3- to 8-fold (females) and 3- to 14-fold (males), the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic in vitro (Ames tests, chromosome aberration tests) or in vivo (mouse micronucleus test).

Fesoterodine had no effect on reproductive function, fertility, or early embryonic development of the fetus at non-maternally toxic doses in mice. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6- to 1.5-fold higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5- to 9-fold higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in mice and rabbits. No dose-related teratogenicity was observed at oral doses up to 75 mg/kg/day in mice (6 to 27 times the expected exposure at the MRHD based on AUC and greater than 77 times the expected C_{max}) and up to 27 mg/kg/day in rabbits (3- to 11-fold by AUC and 19- to 62-fold by C_{max}) or at subcutaneous doses up to 4.5 mg/kg/day in rabbits (9- to 11-fold by AUC and 43- to 56-fold by C_{max}). In mice treated orally with 75 mg/kg/day (6- to 27-times the expected exposure at the MRHD based on AUC and greater than 77-times the expected C_{max}), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45 and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated orally with 27 mg/kg/day (3- to 11-fold by AUC and 19- to 62-fold by C_{max}), incompletely ossified sternbrae (retardation of bone development) were observed in fetuses. In rabbits treated by subcutaneous (sc) administration with 4.5 mg/kg/day (9- to 11-fold by AUC and 43- to 53-fold by C_{max}), maternal toxicity and incompletely ossified sternbrae were observed in fetuses (at an incidence within the background historical range). At 1.5 mg/kg/day s.c., (3-fold by AUC and 11- to 13-fold by C_{max}), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F₁ dams or on the F₂ offspring.

There are no adequate and well-controlled studies using Toviaz in pregnant women. Therefore, Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

It is not known whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

Pediatric Use

The safety and effectiveness of Toviaz in pediatric patients have not been established.

Geriatric Use

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** and **CLINICAL STUDIES** in full prescribing information and **ADVERSE REACTIONS**).

ADVERSE REACTIONS

The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had >10 weeks exposure to Toviaz in these trials.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these 2 studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg.

Table 3 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 mg or 8 mg once daily for up to 12 weeks.

Table 3. Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks' treatment duration

System organ class	Preferred term	Placebo N=554 %	Toviaz 4 mg/day N=554 %	Toviaz 8 mg/day N=566 %
Gastrointestinal disorders	Dry mouth	7.0	18.8	34.6
	Constipation	2.0	4.2	6.0
	Dyspepsia	0.5	1.6	2.3
	Nausea	1.3	0.7	1.9
	Abdominal pain upper	0.5	1.1	0.5
Infections	Urinary tract infection	3.1	3.2	4.2
	Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders	Dry eyes	0	1.4	3.7
Renal and urinary disorders	Dysuria	0.7	1.3	1.6
	Urinary retention	0.2	1.1	1.4
Respiratory disorders	Cough	0.5	1.6	0.9
	Dry throat	0.4	0.9	2.3
General disorders	Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders	Back pain	0.4	2.0	0.9
Psychiatric disorders	Insomnia	0.5	1.3	0.4
Investigations	ALT increased	0.9	0.5	1.2
	GGT increased	0.4	0.4	1.2
Skin disorders	Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Patients also received Toviaz for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator, and reported more than once during the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

OVERDOSAGE

Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

DOSAGE AND ADMINISTRATION

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal insufficiency (CL_{CR} <30 mL/min).
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz is not recommended for use in patients with severe hepatic impairment (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **PRECAUTIONS**).

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed.

Manufactured by:

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The system electrically stimulates the carotid sinus baroreceptors.