

# Investigational Gel, Condom Reduce HIV Spread

BY ROBERT FINN

SAN FRANCISCO — When used intravaginally in combination with a condom, the investigational microbicide PRO 2000/5 gel appeared to reduce HIV transmission by 30% in a large, international, randomized clinical trial.

The finding, which fell short of statistical significance, was seen in a study called HPTN 035 (Phase II/IIb Safety

and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO 2000/5 Gel [P] for the Prevention of HIV Infection in Women). A reduction of 33% would have reached statistical significance, according to Dr. Willard Cates, Jr., president of research at Family Health International, which designed and launched the trial. FHI is a nonprofit foundation in Research Triangle Park, N.C.

The study followed 3,099 women at one U.S. site and at sites in five African countries. All women were given free condoms, HIV risk reduction counseling, and diagnosis and treatment of sexually transmitted diseases. The study participants were then randomized to one of four groups. One-quarter were given PRO 2000/5 gel, one-quarter were given another microbicide called BufferGel, one-quarter were given a placebo gel, and the

remaining women did not receive any gel. The gels were provided as single-use, prefilled applicators and the study participants were instructed to apply one dose of the contents intravaginally up to 60 minutes before each vaginal intercourse. The women were followed for an average of 20 months and were evaluated monthly; 94% of the women completed study visits through the follow-up period.

Participants in the three gel groups reported using the gel during 81% of all sex acts, and nearly all women (99%) said they would use the products if approved for HIV prevention. Women in the three gel groups reported using condoms 72% of the time, and women in the no-gel group reported using condoms 81% of the time.

In all, 194 of the women acquired HIV; 36 women in the PRO 2000/5 group, 54 in the BufferGel group, 51 in the placebo gel group, and 53 among participants who used no gel. This corresponds to an effectiveness rate of 30% for PRO 2000/5; a rate of 33% would have been statistically significant. In a sub-analysis based on reliability of condom use, there was little difference in the infection rate among women who used condoms more than 85% of the time.

However, the infection rate was 4.6 per 100 person-years among the low-condom-use women given the placebo gel compared to 1.0 per 100 person-years among the low-condom-use women given PRO 2000/5 gel. The variation corresponded to an effectiveness rate of 78% for the microbicide.

Dr. Cates acknowledged at a meeting on contraceptive technology sponsored by Contemporary Forums that this post hoc subanalysis did not carry the statistical weight of a primary outcome. "It's not conclusive, not etiologic reasoning in its purest, but at least it's a hint and a ray of hope in a field that was looking for any good news," he said.

Dr. Cates said that a separate trial of PRO 2000/5 gel, involving about 9,000 women, is expected to be completed by the end of 2009, with data available early in 2010.

The investigational microbicide PRO 2000/5 gel (0.5% dose) was developed by Indevus Pharmaceuticals Inc. of Lexington, Mass., and is an entry/fusion inhibitor designed to make it difficult for HIV to attach to and infect healthy cells. The investigational microbicide BufferGel was developed by ReProtect Inc. of Baltimore and is thought to work by boosting the natural acidity of the vagina in the presence of seminal fluid.

The study was funded by the National Institute of Allergy and Infectious Diseases (NCT00074425). Invedus and ReProtect provided the microbicide gels, and the U.S. Agency for International Development provided funding to manufacture BufferGel for the study. Dr. Cates disclosed that he had no conflicts of interest.

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## 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<sub>max</sub>) and up to 27 mg/kg/day in rabbits (3- to 11-fold by AUC and 19- to 62-fold by C<sub>max</sub>) 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<sub>max</sub>). 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<sub>max</sub>), 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<sub>max</sub>), 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<sub>max</sub>), 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<sub>max</sub>), 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 F<sub>1</sub> dams or on the F<sub>2</sub> 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<sub>CR</sub> <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.

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Distributed by: Pfizer Labs, Division of Pfizer Inc, NY, NY 10017

LAB-0381-3.0

Revised November 2008

