International Journal of Impotence Research (2010) 22, 284–289

0955-9930/10
www.nature.com/ijir

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ORIGINAL ARTICLE

# Hardness, function, emotional well-being, satisfaction and the overall sexual experience in men using 100-mg fixed-dose or flexible-dose sildenafil citrate

P Ströberg[1], JC Kaminetsky[2], NC Park[3], ER Goldfischer[4], DL Creanga[5] and VJ Stecher[6]

[1]*Urohålsan/ED-kliniken, Skövde Sweden;* [2]*University Urology Associates, New York, NY, USA;* [3]*Department of Urology, Pusan National University School of Medicine, Pusan, Korea;* [4]*Hudson Valley Urology, PC, Poughkeepsie, NY, USA;* [5]*Contractor to Pfizer Inc, New York, NY, USA and* [6]*Pfizer Inc, New York, NY, USA*

**The prescribing information for sildenafil citrate (VIAGRA, Pfizer, New York, NY, USA) recommends flexible dosing (50 mg initially, adjusted to 100 or 25 mg based on effectiveness and tolerability) in most men with erectile dysfunction (ED). In many men, however, 100 mg may be the most appropriate initial dose because it would reduce the need for titration and could prevent discouragement and treatment abandonment should 50 mg be insufficient. Results of two previously published double-blind, placebo-controlled sildenafil trials of similar design except for a fixed-dose vs flexible-dose regimen were analyzed. Relative to the flexible-dose, approximately one-third more men were satisfied with an initial and fixed dose of 100 mg. In addition, tolerability was similar, and improvements from baseline in outcomes on validated, ED-specific, patient-reported questionnaires were either similar (erectile function and the percentage of completely hard and fully rigid erections) or greater (emotional well-being and the overall sexual experience). The similarity in outcomes is not surprising given that almost 90% of the men in the flexible-dose trial titrated to 100 mg after 2 weeks. These data suggest prescription of an initial dose of 100 mg for men with ED, except in those for whom it is inappropriate.**
*International Journal of Impotence Research* (2010) **22,** 284–289; doi:10.1038/ijir.2010.17;
published online 1 July 2010

**Keywords:** erectile dysfunction; quality of life; sildenafil

## Introduction

For most men with erectile dysfunction (ED), the prescribing information for sildenafil citrate (VIAGRA, Pfizer) recommends an initial dose of 50 mg, increased to 100 mg or decreased to 25 mg based on effectiveness and tolerability (flexible dose).[1] However, 100 mg sildenafil produced optimal erection hardness (fully hard and rigid) in a substantial proportion of men with ED.[2] In addition, in dose-optimization studies[3,4] and at the end of double-blind, placebo-controlled (DBPC) treatment in recent reports of flexible-dose trials,[5,6] 100 mg was the dose that was used by most men. Thus, the 100-mg dose may provide some additional benefit beyond that achieved with the 50-mg dose and may be the most appropriate choice for initiation of therapy in many men.

This report assesses erection hardness, erectile function, emotional well-being, satisfaction (disease related and treatment related) and the overall sexual experience in men treated with 100 mg fixed-dose sildenafil and in men treated with flexible-dose sildenafil (50 and 100 mg), using data from two DBPC trials that were similarly designed except for a fixed-dose vs flexible-dose regimen.[7,8] The objective was to assess the efficacy and tolerability of an initial dose of sildenafil 100 mg relative to the flexible-dosage regimen recommended in the prescribing information.

## Materials and methods

One trial was a multinational (Republic of Korea, Russian Federation, Spain and Sweden), parallel-group, randomized (1:1:1) DBPC trial of fixed-dose sildenafil (50 or 100 mg) or placebo administered on demand over an 8-week treatment period.[7] The other trial was a multicenter (United States),

Correspondence: Dr P Ströberg, MD, Urohålsan/ED-kliniken, Långgatan 18 54131, Skövde Sweden.
E-mail: peter.stroeberg@telia.com
Received 22 January 2010; revised 6 May 2010; accepted 23 May 2010; published online 1 July 2010

parallel-group, randomized (1:1) DBPC trial of flexible-dose sildenafil (50 or 100 mg) administered on demand over a 10-week treatment period.[8] In both trials, $\leqslant 1$ dose of study medication was to be taken per day. Details of the patients and methods of the two trials have been published previously.[7,8]

As described previously,[7,8] several efficacy assessments were conducted, including the Erection Hardness Score (EHS[9]), the International Index of Erectile Function (IIEF),[10] the Self-Esteem And Relationship (SEAR) questionnaire,[11–13] the Sexual Experience Questionnaire (SEX-Q),[14] the Quality of Erection Questionnaire,[15] the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS)[16] and three global efficacy assessment questions. Except for the global efficacy assessment questions, all assessment tools are validated, and a higher score indicates better outcome. Safety data included all adverse events (AE) reports from the original trials.

In this study, analyses were conducted on data from the intent-to-treat population for each study, which was defined as men who took at least one dose of study medication and who provided sufficient efficacy data for at least one efficacy analysis. Treatment effects were estimated using least square means from an analysis of covariance model for change scores from baseline to DBPC end of treatment on the IIEF, SEAR and SEX-Q, and the end-of-treatment EDITS Index score. The model used terms of baseline value, treatment group, investigator site and prognostic factors (age, ED duration, ED etiology) with *P* values calculated at the 5% significance level for the test of treatment group differences. Logistic regression (terms of treatment group, age, ED duration and ED etiology) was used to analyze the proportion of men who were satisfied with treatment (dichotomized EDITS score). The percentages of EHS 3, EHS 4 and EHS 3 or 4 erections based on all of the event log data since the previous visit were analyzed as clustered binomial data using a logistic regression (terms for baseline percentage, treatment group, age, ED duration and ED etiology), with a scale adjustment for overdispersion (estimated by Williams method) and model; treatment effects were estimated using predicted percentages from the model. Pearson correlations were computed between the SEX-Q change from baseline scores and all other outcomes (change from baseline or end of treatment); 95% confidence intervals for the correlation coefficient were constructed using Fisher's *Z*-transformation.

## Results

*Population and exposure*

In both trials, each treatment group comprised ~100 men, most of whom had ED that was of organic or mixed etiology and that was mild to moderate in severity (Table 1).

At week 2, 88% (92/104) of patients randomized to flexible-dose sildenafil and 92% (97/105) randomized to flexible-dose placebo increased their dose

**Table 1** Baseline characteristics (intent-to-treat population)

| | *Fixed dose* | | | *Flexible dose* | |
|---|---|---|---|---|---|
| | *Placebo (n = 95)* | *Sildenafil 50 mg (n = 94)* | *Sildenafil 100 mg (n = 99)* | *Placebo (n = 105)* | *Sildenafil 50 and 100 mg (n = 104)* |
| Mean age ± s.d. (years) | 50 ± 10 | 52 ± 10 | 51 ± 10 | 51 ± 12 | 53 ± 12 |
| *Race (%)* | | | | | |
| White | 65 | 63 | 64 | 74 | 83 |
| Black | 0 | 0 | 0 | 13 | 8 |
| Asian | 35 | 37 | 35 | 0 | 2 |
| Other | 0 | 0 | 1 | 12 | 8 |
| Mean ED duration (range) (years) | 3.2 (<1–29) | 3.2 (<1–26) | 3.3 (<1–19) | 3.8 (<1–13) | 4.6 (<1–41) |
| *ED etiology (%)* | | | | | |
| Mixed/organic/psychogenic | 56/28/16 | 59/29/13 | 63/24/13 | 24/58/18 | 26/58/16 |
| ED severity, (%) | 16 | 27 | 14 | 28 | 33 |
| *Current comorbidities (%)* | | | | | |
| Hypertension | 20 | 21 | 19 | 41 | 38 |
| Hypercholesterolemia | 7 | 7 | 2 | 21 | 24 |
| Benign prostatic hyperplasia | 9 | 15 | 12 | 17 | 16 |
| Diabetes | 8 | 9 | 13 | 17 | 15 |
| Hyperlipidemia | 6 | 7 | 2 | 10 | 9 |
| Depression | 1 | 2 | 1 | 9 | 10 |
| Coronary artery disease | 0 | 0 | 0 | 3 | 5 |

Abbreviation: ED, erectile dysfunction.

from 50 mg to 100 mg; at the end of the DBPC treatment, 87% (90/104) and 92% (97/105), respectively, remained on the higher dose. During the DBPC phase of each trial, patients in each treatment group received an average of seven or eight doses per month. Across both trials, only one man discontinued sildenafil (flexible dose) because of lack of efficacy and only two men discontinued sildenafil because of treatment-related AEs: moderate dyspepsia (100-mg fixed dose) and moderate headache (100-mg flexible dose).

*Efficacy*

Sildenafil, whether initiated at a fixed dose of 50 or 100 mg, or initiated at a dose of 50 mg and titrated as needed up to 100 mg, was significantly more effective than placebo (Table 2). The 100-mg fixed dose was significantly more effective than the 50-mg fixed dose in improving the IIEF Overall Satisfaction domain score; the SEAR Sexual Relationship Satisfaction domain, Overall Relationship Satisfaction subscale and Total scores; all SEX-Q domain scores; and the SEX-Q total score (Table 2). In addition, the EDITS Index was significantly higher in the fixed-dose sildenafil 100-mg group vs the fixed-dose sildenafil 50-mg group, although the difference between the dosage groups in the estimated percentage of men who were satisfied with sildenafil treatment (dichotomized EDITS scores: 93 vs 88%) was not statistically significant (Table 2).

For the fixed-dose sildenafil 100-mg group relative to the flexible-dose sildenafil group (Table 2), there was a similar improvement from baseline in the percentage of EHS 4 erections (33 and 35%, respectively), EHS 3 or 4 erections (36 and 35%, respectively) and IIEF scores ($\leqslant$1 point difference

**Table 2** Efficacy outcomes

| | *Fixed dose* | | | *Flexible dose* | |
|---|---|---|---|---|---|
| | *Placebo* (n = *95*) | *Sildenafil 50 mg* (n = *94*) | *Sildenafil 100 mg* (n = *99*) | *Placebo* (n = *105*) | *Sildenafil 50 and 100 mg* (n = *104*) |
| *EHS occasions, % at baseline/estimated % with treatment* | | | | | |
| EHS 3 | 34/39 | 25/47 | 42/41 | 41/40 | 41/33 |
| EHS 4 | 2/7 | 1/25* | 2/35* | 7/9 | 4/39* |
| EHS 3 or EHS 4 | 35/47 | 26/77* | 45/81* | 48/52 | 44/79* |
| *LS mean change in IIEF domain score ± s.e.*[a] | | | | | |
| Erectile Function, range 1–30 | 2.1 ± 0.7 | 7.7 ± 0.7* | 9.1 ± 0.6* | 2.2 ± 0.9 | 8.0 ± 0.9* |
| Intercourse Satisfaction, range 0–15 | 1.7 ± 0.3 | 3.7 ± 0.3* | 4.3 ± 0.3* | 1.9 ± 0.5 | 3.4 ± 0.5** |
| Orgasmic Function, range 0–10 | 0.5 ± 0.3 | 1.8 ± 0.3*** | 2.1 ± 0.3* | 0.3 ± 0.4 | 1.8 ± 0.4* |
| Overall Satisfaction, range 2–10 | 0.3 ± 0.2 | 2.2 ± 0.2* | 3.0 ± 0.2*,**** | 0.7 ± 0.3 | 2.3 ± 0.3* |
| Sexual Desire, range 2–10 | 0.3 ± 0.2 | 0.9 ± 0.2** | 1.2 ± 0.2* | 0.4 ± 0.2 | 0.8 ± 0.2 |
| *LS mean change in SEAR score ± s.e., range 0–100*[a] | | | | | |
| Sexual Relationship Satisfaction | 4.3 ± 2.5 | 26.6 ± 2.5* | 34.4 ± 2.4*,**** | 7.0 ± 2.8 | 23.5 ± 2.8* |
| Confidence | 0.3 ± 2.5 | 21.9 ± 2.5* | 27.9 ± 2.5* | 5.7 ± 2.7 | 16.9 ± 2.8*** |
| Self-Esteem | 1.3 ± 2.6 | 23.4 ± 2.6* | 27.8 ± 2.5* | 7.6 ± 2.9 | 19.5 ± 2.9*** |
| Overall Relationship Satisfaction | –1.0 ± 3.0 | 19.1 ± 3.0* | 28.0 ± 2.9*,**** | 2.6 ± 3.8 | 11.8 ± 3.8** |
| Overall | 2.5 ± 2.4 | 24.7 ± 2.4* | 31.6 ± 2.4*,**** | 6.4 ± 2.6 | 20.8 ± 2.6* |
| *LS mean change in SEX-Q score ± s.e., range 0–100*[a] | | | | | |
| Erection domain | 6.8 ± 2.6 | 32.0 ± 2.5* | 39.4 ± 2.5*,**** | 8.7 ± 3.1 | 31.7 ± 3.1* |
| Individual Satisfaction domain | 4.5 ± 2.4 | 22.9 ± 2.3* | 28.7 ± 2.3*,**** | 7.0 ± 2.7 | 21.7 ± 2.7* |
| Couples Satisfaction domain | 5.0 ± 2.5 | 23.4 ± 2.5* | 30.8 ± 2.5*,**** | 9.7 ± 3.0 | 28.5 ± 3.0* |
| Total score | 5.8 ± 2.4 | 27.6 ± 2.3* | 34.5 ± 2.3*,**** | 8.6 ± 2.7 | 28.5 ± 2.8* |
| *EDITS* | | | | | |
| LS mean Index ± s.e., range 0–100 | 49.7 ± 2.1 | 73.0 ± 2.0* | 78.4 ± 2.0*,**** | 49.6 ± 3.2 | 66.5 ± 3.3* |
| Dichotomized, estimated % satisfied (odds ratio vs placebo)[b] | 46 | 88 (8.7)* | 93 (14.7)* | 46 | 69 (2.6)*** |

Abbreviations: EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; EHS, Erection Hardness Score (EHS 3 = hard enough for penetration but not completely hard; EHS 4 = completely hard and fully rigid); IIEF, International Index of Erectile Function; LS, least squares; SEX-Q, Sexual Experience Questionnaire; SEAR, Self-Esteem And Relationship questionnaire.

[a]Change from baseline.

[b]Dichotomized as satisfied (index >50) vs unsatisfied (index $\leqslant$50).

*$P<0.0001$ vs placebo.

**$P<0.05$ vs placebo.

***$P<0.001$ vs placebo.

****$P<0.05$ vs sildenafil 50 mg.

**Table 3** Correlations with the change in score from baseline on the SEX-Q total score

| | *Pearson correlation coefficient (95% CI)* | |
|---|---|---|
| | *Fixed-dose sildenafil 50 or 100 mg vs placebo for 8 weeks* | *Flexible-dose sildenafil 50 and 100 mg vs placebo for 10 weeks* |
| *IIEF change in domain score* | | |
| Erectile Function | 0.80 (0.76–0.84)* | 0.84 (0.80–0.88)* |
| Intercourse Satisfaction | 0.72 (0.66–0.77)* | 0.72 (0.65–0.78)* |
| Orgasmic Function | 0.58 (0.49–0.65)* | 0.57 (0.47–0.66)* |
| Overall Satisfaction | 0.76 (0.70–0.80)* | 0.77 (0.71–0.83)* |
| Sexual Desire | 0.37 (0.27–0.47)* | 0.54 (0.43–0.63)* |
| EDITS Index[a] | 0.85 (0.81–0.88)* | 0.86 (0.82–0.89)* |
| *EHS change in percentage occasions* | | |
| EHS 3 | 0.20 (0.08–0.31)** | 0.14 (0.00–0.28) |
| EHS 4 | 0.57 (0.48–0.65)* | 0.68 (0.60–0.75)* |
| EHS 3 or EHS 4 | 0.70 (0.63–0.76)* | 0.76 (0.69–0.82)* |
| *SEAR change in component score* | | |
| Sexual Relationship Satisfaction | 0.87 (0.84–0.90)* | 0.88 (0.84–0.91)* |
| Confidence | 0.79 (0.74–0.83)* | 0.60 (0.50–0.68)* |
| Self-Esteem | 0.73 (0.67–0.78)* | 0.55 (0.44–0.64)* |
| Overall Relationship Satisfaction | 0.72 (0.66–0.77)* | 0.48 (0.36–0.58)* |
| Overall | 0.88 (0.84–0.90)* | 0.83 (0.78–0.87)* |

Abbreviations: EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; EHS, Erection Hardness Score; IIEF, International Index of Erectile Function; SEAR, Self-Esteem And Relationship questionnaire; SEX-Q, Sexual Experience Questionnaire.
[a]EDITS Index outcome was from the end of treatment, whereas other outcomes were changes from baseline.
*$P<0.0001$.
**$P=0.001$.

between the groups across IIEF domains). However, for the fixed-dose sildenafil 100-mg group relative to the flexible-dose sildenafil group there was a greater improvement from baseline in SEAR scores (8–16 point difference between the groups across SEAR components) and in SEX-Q scores (3–7 point difference between the groups across SEX-Q domains), a greater least square mean ± s.e. EDITS Index (78.4 ± 2.0 and 66.5 ± 3.3, respectively), and a larger estimated percentage of men who were satisfied with sildenafil treatment (dichotomized EDITS scores: 93 vs 69%). The SEX-Q total score, which assesses the sexual experience overall in the domains of erection, individual satisfaction and couples satisfaction, correlated positively with all other outcomes in both trials (Table 3).

*Safety*

In both trials, most AEs were mild or moderate in severity. The most frequently reported AEs were flushing, dyspepsia, headache and nasal congestion in the fixed-dose trial, which occurred at similar frequencies in the sildenafil 50-mg and 100-mg groups, and flushing, headache, nasal congestion and dizziness in the flexible-dose trial (Table 4). No treatment-related serious or severe AEs were reported in the sildenafil arms.

**Table 4** Most frequently (>2% of patients) reported all-causality adverse events during the double-blind, placebo-controlled phase of the trials

| | *Fixed dose* | | | *Flexible dose* | |
|---|---|---|---|---|---|
| *Adverse event, n*[a] | *Placebo (n = 95)* | *Sildenafil 50 mg (n = 94)* | *Sildenafil 100 mg (n = 99)* | *Placebo (n = 105)* | *Sildenafil 50 and 100 mg (n = 104)* |
| Flushing | 0 | 5 | 5 | 2 | 16 |
| Headache | 3 | 1 | 3 | 6 | 14 |
| Nasal congestion | 0 | 2 | 3 | 2 | 5 |
| Dizziness | 0 | 0 | 0 | 0 | 3 |
| Dyspepsia | 0 | 1 | 3 | 2 | 2 |

[a]All events were of mild or moderate severity in the sildenafil groups.

## Discussion

As reported previously, sildenafil, whether initiated at a fixed dose of 50 or 100 mg,[7] or at a dose of 50 mg and titrated as needed up to 100 mg,[8] was significantly more effective than placebo in the treatment of ED, and there were additional benefits to the use of 100 mg fixed-dose sildenafil compared with 50 mg fixed-dose sildenafil.[8] Although definitive statements about the comparative efficacy of 100-mg

fixed-dose sildenafil and the flexible-dose sildenafil regimen are limited by the fact that the regimens were not compared within a controlled trial and the protocols of the two trials collated herein were not identical, the results of the current collated report suggest that an initial dose of sildenafil 100 mg is at least as effective and well tolerated as an initial dose of 50 mg with the option to titrate as needed. Definitive statements about the comparative tolerability of 100-mg fixed-dose sildenafil and the flexible-dose sildenafil regimen are also limited by the collated nature of the data presented in this report, although the low rate of discontinuation because of treatment-related AEs suggests that both regimens are generally well tolerated. The results of the current report are generalizable to the population of men with ED.

For the 100-mg fixed-dose regimen relative to the flexible-dose regimen, there was a similar increase from baseline in the percentage of EHS 4 erections and EHS 3 or 4 erections, a similar improvement from baseline in IIEF scores, a greater improvement from baseline in SEAR scores and SEX-Q scores, and a higher EDITS Index; approximately one-third more men in the 100-mg fixed-dose vs the flexible-dose regimen were satisfied with their sildenafil treatment. The similarity in outcomes between the two regimens is not surprising given that almost 90% of the men who initiated treatment with flexible-dose sildenafil titrated to a dose of 100 mg after 2 weeks. The apparent difference in outcomes on the SEAR, SEX-Q and EDITS between the two regimens may represent cultural differences between the European and Asian population treated with 100 mg fixed-dose sildenafil and the US (mainly white) population treated with flexible-dose sildenafil. The SEAR, SEX-Q and EDITS assess health-related quality-of-life concepts, which are likely to be more susceptible to cultural differences than are more functional concepts, such as those assessed by the EHS and IIEF. Cultural differences on SEAR responses were published previously.[13,17]

Given that almost 90% of the men who initiated treatment with flexible-dose sildenafil titrated to a dose of 100 mg after 2 weeks, initiating treatment with 100-mg sildenafil should greatly decrease the need for dose titration and, in those men for whom a dose of 50 mg might prove ineffective, may decrease the risk of discouragement and treatment abandonment because of inadequate dosing. The high proportion of men titrating to a dose of 100 mg supports earlier results, which showed that 100-mg sildenafil produced optimal erection hardness (fully hard and rigid) in a substantial proportion of men with ED[2] and that 100 mg was the dose used by most men in dose-optimization studies.[3,4,6] Several studies reported that titration to the highest well-tolerated approved dose and/or early dose optimization contributed to treatment success.[6]

Treatment optimization, which includes selecting the most appropriate dose, '…may promote treatment adherence and thus facilitate optimal patient outcomes.'[6] Some patients who are prescribed sildenafil for ED in the clinical practice setting neither refill their initial prescription nor seek alternative therapies.[18,19] For example, an analysis of sildenafil use during the first 24 weeks of availability at a large health maintenance organization revealed that only 61% of patients filled a second sildenafil prescription within 3 months of their first prescription.[20] In addition, in a large dose-optimization study in which sildenafil was initiated at a dose of 50 mg for 4 weeks according to the package instructions, 14% (153/1109) failed to return for the second visit for scheduled dosage optimization.[6] In several studies, incorrect administration, including suboptimal dosing, was the most frequent cause of nonresponse to sildenafil.[6]

An initial dose of sildenafil 100 mg may not be appropriate in some men. For example, higher plasma concentrations of sildenafil than those seen in healthy young volunteers occurred in men aged >65 years, in those who have hepatic impairment (for example, cirrhosis) or severe renal impairment (for example, creatinine clearance $<30\,ml\,min^{-1}$), and in those using concomitant potent cytochrome P450 3A4 inhibitors (for example, ketoconazole, itraconazole, erythromycin, saquinavir).[1,21–23] Because ritonavir greatly increased the systemic level of sildenafil in a study of healthy volunteers not infected with the human immunodeficiency virus, it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48-h period.[1,23] In addition, men with left ventricular outflow obstruction (for example, aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators, including sildenafil.[1] When sildenafil is coadministered with an α-blocker, patients should be stable on α-blocker therapy before initiating sildenafil treatment, and sildenafil should be initiated at the lowest dose.[1,24]

In conclusion, sildenafil in doses of 50 and 100 mg is effective for the treatment of ED, and both doses are generally well tolerated. An initial dose of sildenafil 100 mg appears to be at least as efficacious and well tolerated as an initial dose of 50 mg with the option to titrate to the optimal dose. Furthermore, an initial dose of 100 mg may reduce the need for dose titration and may prevent discouragement and treatment abandonment in men for whom a dose of 50 mg is insufficient. This suggests prescription of an initial dose of 100 mg, except in those for whom it is inappropriate.

## Conflict of interest

Peter Ströberg is a scientific study/trial investigator for Pfizer. Jed C. Kaminetsky is a consultant/advisor for Pfizer and Slate Pharmaceuticals; a meeting participant/lecturer for Astellas, Auxilium, Boehringer Ingelheim,

GlaxoSmithKline, Lilly, Pfizer, and Solvay; and a scientific study/trial investigator for Aeterna Zentaris, Astellas, Auxilium, Indevas, Lilly, Pfizer, Plethora Solutions, and Spectrum. Nam Cheol Park has nothing to declare. Evan R. Goldfischer is a consultant/advisor for Astellas; a clinical trial investigator for Amgen, Astellas, Bayer, GlaxoSmithKline, Indevus, Lilly, Johnson & Johnson, Merck, Novartis, Pfizer, Ortho McNeil, Sanofi, Schering-Plough, Schwartz, and Unimed; and a lecturer for Astellas, Auxilium, Bayer, GlaxoSmithKline, Indevus, Lilly, and Pfizer. Dana L. Creanga was a paid consultant to Pfizer in connection with the statistical analyses performed in this study. Vera J. Stecher is an employee of Pfizer.

## Acknowledgments

These studies were funded by Pfizer Inc. Editorial support was provided by Deborah M Campoli-Richards, BSPHA, RPh, at Complete Healthcare Communications, Inc and was funded by Pfizer.

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