THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

PHARMACOTHERAPY

Effectiveness and Safety of Oro-Dispersible Sildenafil in a New Film Formulation for the Treatment of Erectile Dysfunction: Comparison Between Sildenafil 100-mg Film-Coated Tablet and 75-mg Oro-Dispersible Film

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ABSTRACT

Background: A new oro-dispersible film (ODF) formulation of sildenafil has been developed for the treatment of erectile dysfunction (ED) to overcome the drawbacks that some patients experience when taking the conventional film-coated tablet (FCT).

Aim: To assess the effectiveness and safety of sildenafil ODF formulation in patients with ED who were using the conventional FCT.

Methods: From May 2017 through July 2017, 139 patients with ED were enrolled. Data from penile color-duplex ultrasound, medical history, hormonal evaluation, and patient self-administered questionnaires were collected. All patients were administered sildenafil 100-mg FCT for 4 weeks. Thereafter, they underwent a 2-week washout period and subsequently took sildenafil 75-mg ODF for 4 weeks.

Outcomes: The International Index of Erectile Function (IIEF-15), Hospital Anxiety and Depression Scale (HADS), Patient Global Impressions of Improvement (PGI-I), and Clinician Global Impressions of Improvement (CGI-I) questionnaires were administered and severity of ED was classified as severe (IIEF-15 score ≤ 10), moderate (IIEF-15 score 11−16), or mild (IIEF-15 score = 17−25).

Results: All patients completed the final protocol. Differences in mean IIEF scores for erectile function, orgasmic function, sexual desire, and intercourse satisfaction were significantly in favor of sildenafil 100-mg FCT, whereas the mean score for overall satisfaction was in favor of sildenafil 75-mg ODF. A significant difference in changes in HADS score was found from washout to final follow-up (mean difference = −0.19; $P < .01$). For the ODF formulation, the median CGI-I score was 3.5 (interquartile range [IQR] = 2.5−4.5) and the median PGI-I score was 3.0 (IQR = 2.0−4.0). The median action time was 20.0 minutes (IQR = 15.0−30.0) and the median mouth time was 60.0 seconds (IQR = 30.0−120.0).

Clinical Implications: The ODF formulation of a widely known drug, with the same safety and effectiveness of the FCT, was better appreciated by patients in overall satisfaction.

Strengths and Limitations: This is the first clinical trial to assess the efficacy of a new formulation of sildenafil in patients with ED. The limitations of the study are related to the methodology used: it was not a case-control study and the patients were not drug-naïve for ED treatment. Therefore, only the "additional" side effects of the ODF formulation compared with FCT are reported.

Received July 31, 2017. Accepted October 24, 2017.

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https://doi.org/10.1016/j.jsxm.2017.10.066

Conclusion: The new ODF formulation is as efficient and safe as the FCT formulation and offers a new choice of treatment to specialists for more precisely tailored therapy. **Cocci A, Capece M, Cito G, et al. Effectiveness and Safety of Oro-Dispersible Sildenafil in a New Film Formulation for the Treatment of Erectile Dysfunction: Comparison Between Sildenafil 100-mg Film-Coated Tablet and 75-mg Oro-Dispersible Film. J Sex Med 2017;14:1606−1611.**

Key Words: Erectile Dysfunction; Impotence; Sildenafil Citrate; Therapeutics

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to obtain or maintain an erection sufficiently rigid for achieving satisfactory sexual performance.[1] It affects nearly 50% of men older than 40 years, causing patients serious distress and prompting them to seek medical opinions they might not otherwise seek.[2]

ED has a significant impact on the quality of life of patients because it influences the self-perception and sexuality of those men and might undermine their interactions with women or potential partners.[3] Because sexual satisfaction is considered a major predictor of life satisfaction, treatment of ED would likely improve the quality of life for these patients and their partners.[4]

Many therapeutic options are available for the treatment of ED. One option is the use of phosphodiesterase type 5 inhibitors (PDE5is). PDE5is, including sildenafil, tadalafil, vardenafil, and avanafil, are currently approved for use in ED and each has an individual pharmacokinetic and side effects profile, although no significant differences in efficacy among therapies are evident.[1,5−8]

Sildenafil, the first approved PDE5i, is a safe and effective oral agent for the treatment of ED and is predominantly metabolized by cytochrome P-450 into an *N*-desmethyl metabolite (*N*-desmethyl sildenafil) that accounts for approximately 1 fifth of the drug's activity.[9,10]

Oral administration of a tablet can lead to 2 types of effects. (i) The original formulation is inconvenient for patients because water is required for the medicine to be taken. (ii) Oral administration of the tablet relies on the patient's ability to swallow the dosage safely, which could be problematic for individuals who have swallowing disorders. Dysphagia has an estimated of 22% in patients older than 50 years.[11] To overcome these drawbacks, a new oro-dispersible film (ODF) formulation was developed. It is quickly dispersed in the mouth and can be administered without water.[12]

According to the Biopharmaceutics Classification System, sildenafil is classified as a class II drug substance (high permeability and low solubility). The new sildenafil ODF formulation, developed by IBSA (Lugano, Switzerland), is approved in Europe at doses of 25, 50, 75, and 100 mg. Each sildenafil 75-mg ODF contains sildenafil citrate 105.3 mg, equivalent to sildenafil 75 mg, in the form of a rectangular, flexible, opaque, light-blue film measuring 40 × 45 mm, whereas each sildenafil 100-mg film-coated tablet (FCT) contains sildenafil citrate 140.4 mg, equivalent to sildenafil 100 mg. A previous study compared the 2 treatments with the same active substance but with different dosages and different formulations. It was a non-inferiority study of the 2 treatments for effectiveness, not for bioequivalence.[13] The ODF formulation is an innovative patented product developed in accordance with EP 1689374 (self-supporting films for pharmaceutical and food use) and WO 2014/049548 (ODFs with quick dissolution times for therapeutic and food use).[13]

We evaluated the efficacy and safety of the sildenafil ODF formulation in patients with ED who were taking the conventional sildenafil FCT.

METHODS

From May 2017 through July 2017, we enrolled 139 patients with a history of chronic ED. The etiology of ED was determined, in all cases, by a standard protocol involving penile color-duplex ultrasound, complete medical history, hormonal evaluation, and patient self-administered questionnaires on sexual function. We measured serum concentrations of follicle-stimulating hormone (normal range = 1.5−8.0 IU/L), prolactin (3.0−18 ng/mL), thyroid-stimulating hormone (0.3−5.5 mIU/L), luteinizing hormone (1.8−12 IU/L), and total testosterone (2.7−18 ng/mL).

Inclusion criteria were heterosexual men younger than 75 years, presence of ED evaluated through the International Index of Erectile Function (IIEF), sexual intercourse at least 2 times per week, an Eastern Cooperative Oncology Group (ECOG) scale of performance status score no higher than 1, absence of moderate or severe cardiovascular diseases, and moderate ED according to penile dynamic Doppler examination. All patients enrolled in the study were eligible for first-line therapy of ED based on PDE5i, according to European Association of Urology, American Urological Association, and International Society for Sexual Medicine guidelines. Exclusion criteria were being unable or unwilling to provide informed consent, an IIEF score lower than 16, presence of unstable coronary artery disease (ECOG score > 1), sexual intercourse no more than 1 time per week, concomitant use of nitrates in any form, and known hypersensitivity to sildenafil or its components. Men with ED based on neurogenic, hormonal, or anatomic conditions and those who underwent previous surgical treatment of the penis or pelvic area were excluded from the study.

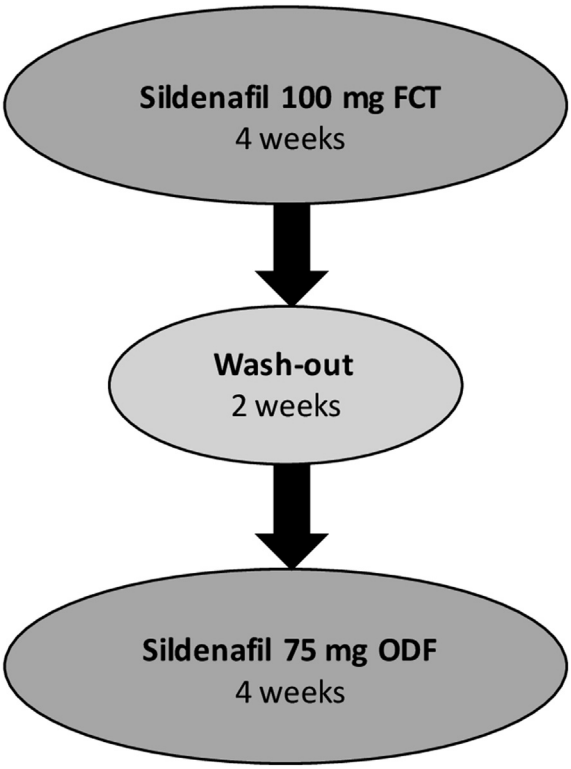

Figure 1. Study protocol. FCT = film-coated tablet; ODF = orodispersible film.

In the study protocol (Figure 1), all patients were administered sildenafil 100-mg FCT for 4 weeks. After a 2-week washout period from sildenafil 100-mg FCT, all patients enrolled were asked to take sildenafil 75-mg ODF alone (Rabestrom; IBSA). They took the drug on demand, but they were asked to perform sexual intercourse at least 2 times a week. For the FCT, patients were told to take the tablet on an empty stomach 45 to 60 minutes before approaching the partner. For the ODF, patients were instructed to put the film under the tongue or underneath the palate, according to their preference.

Briefly, the preparation process of sildenafil 75-mg ODF according to the WO 2014/049548 patent consists of the following steps. Maltodextrin, a plasticizer (propylene glycol), the active ingredient (sildenafil citrate), and the other excipients are solubilized or dispersed in water; the mixture is coated onto a release liner and dried in the oven at controlled temperature, air circulation and coating speed; the dried mass is cut into reels; and the films are punched, pouched, and sealed in suitable single-dose sachets.

The impact of sildenafil on sexual function was evaluated by a follow-up physician interview and patient self-administered questionnaires. During the study protocol, the IEF-15 and the Hospital Anxiety and Depression Scale (HADS) were administered to all patients. The IIEF-15 scale classified the severity of ED as severe (IIEF-15 score $\leq$ 10), moderate (IIEF-15 score = 11−16), or mild (IIEF-15 score = 17−25).[14] It covered the domains of patients' treatment response and satisfaction, partner's treatment satisfaction, comparative previous treatment satisfaction, adverse effects, and patient and partner quality of life. The item on patient treatment response was rated on a scale of 1 to 5, with scores of 4 and 5 indicating complete satisfactory sexual intercourse on most occasions and almost always, respectively. The IIEF-15 sub-scores were rated: erectile function (IIEF-EF), orgasmic function (IIEF-OF), sexual desire (IIEF-SD), intercourse satisfaction (IIEF-IS), and overall satisfaction (IIEF-OS). The HADS was used to determine levels of anxiety and depression that a patient was experiencing on a scale of 0 to 21 as normal (0−7), borderline abnormal (8−10), or abnormal (11−21). Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I) scales were completed to evaluate patient satisfaction after drug administration. PGI-I estimated the score that best described the

Table 1. Baseline characteristics of the population (N = 139)

Variables	
Age (y), median (IQR)	66.6 (63.3−69.0)
BMI (kg/m^2), median (IQR)	14.0 (12.0−16.0)
IIEF domain scores, median (IQR)	
Erectile function	14.0 (12.0−17.0)
Orgasmic function	3.0 (2.0−5.0)
Sexual desire	3.0 (2.0−3.0)
Intercourse satisfaction	4.0 (3.0−6.0)
Overall satisfaction	6.0 (4.0−7.0)
Classification of ED, n (%)	
Severe	19 (13.7)
Moderate	65 (46.8)
Mild	55 (39.6)
HADS score, median (IQR)	5.0 (5.0−6.0)
Hypertension, n (%)	81 (58.3)
Diabetes, n (%)	31 (22.3)
Hyperlipidemia, n (%)	46 (33.1)
Hearth disease, n (%)	23 (16.5)
Smoking, n (%)	
No	29 (20.9)
Former	82 (59.0)
Current	28 (20.1)
Alcohol, n (%)	
Abstinent	84 (60.4)
Light	55 (39.6)
Previous penile surgery, n (%)	16 (11.5)
Duration of erectile dysfunction, n (%)	24.0 (12.0−48.0)
FSH (IU/L), median (IQR)	5.0 (1.9−8.0)
LH (IU/L), median (IQR)	5.6 (1.2−11)
TT (ng/mL), median (IQR)	7.7 (3−15)
TSH (mIU/L), median (IQR)	2.5 (0.8−5.2)
PRL (ng/mL), median (IQR)	6.6 (4−16)

BMI = body mass index; ED = erectile dysfunction; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; IQR = interquartile range; LH = serum luteinizing hormone; MBI = body max index; PRL = prolactin; TSH = thyroid-stimulating hormone; TT = total testosterone.

Table 2. Mean changes of variables from baseline to washout and final follow-up

Variables	From baseline to washout	From washout to final follow-up	Sildenafil 100-mg FCT vs 75-mg ODF
IEEF score, mean (SD)			
Erectile function	−10.46 (3.43)*	9.71 (3.60)*	−0.74 (1.44)*
Orgasmic function	−3.63 (2.42)*	3.07 (2.42)*	−0.56 (1.12)*
Sexual desire	−4.37 (2.12)*	4.06 (1.83)*	−0.30 (1.51)†
Intercourse satisfaction	−6.81 (3.48)*	5.12 (4.75)*	−1.68 (3.90)*
Overall satisfaction	−0.41 (0.91)*	1.12 (2.55)*	0.71 (2.65)*
Overall satisfaction	−0.41 (0.91)*	1.12 (2.55)*	0.71 (2.65)*
HADS score, mean (SD)	1 (0.5)*	−0.8 (0.55)*	0.1 (0.05)

FCT = film-coated tablet; HADS = Hospital Anxiety and Depression Scale; IIEF = International Index of Erectile Function; ODF = oro-dispersible film.
*$P < .01$; †$P < .05$.

postoperative condition, from 1 (very much better) to 7 (very much worse). The CGI-I was used to evaluate the response to the question, "Compared to his condition at baseline, how much has he changed?" (1 = very much improved to 7 = very much worse).

Each patient signed a written fully informed consent statement before being enrolled in the study. Institutional review board approval was not necessary because the study concerned a drug already widely known and used for ED, but only in a new formulation.

Mouth time (seconds) was measured as the time from ingestion to final dissolution of the drug. Action time (minutes) was measured as the time from ingestion to erection after sexual stimulation.

Data were analyzed using standard descriptive statistics, the Student t-test, and linear regression with IBM SPSS 20.0 (IBM Corp, Armonk, NY, USA).

RESULTS

139 patients completed the final protocol. The baseline characteristics of patients at enrollment are presented in Table 1. For patient history, 16 patients (11.5%) underwent previous penile surgery, 5 of whom (3.6%) underwent a penile frenuloplasty, 9 (6.5%) underwent a circumcision for a tightened phimosis, and 2 (1.4%) underwent surgical removal of penile condyloma. At baseline, all hormonal parameters were in the normal range in the 2 groups and were not related to the

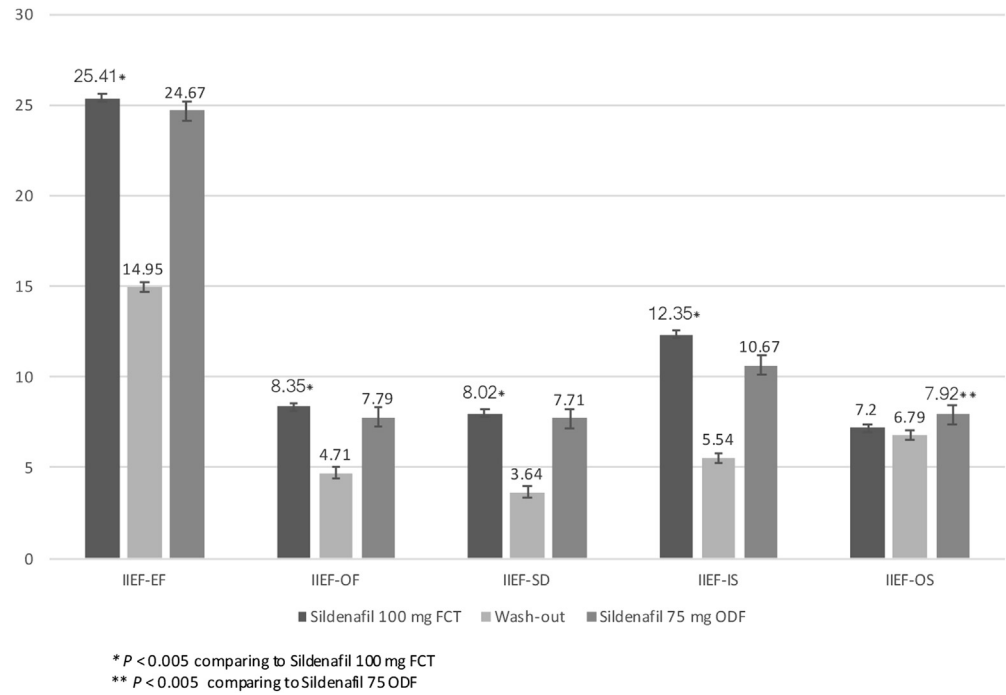

Figure 2. Changes of IIEF-15 from baseline to washout and final follow-up ($P < .005$ by χ^2 test). FCT = film-coated tablet; IIEF-EF = International Index of Erectile Function erectile function domain; IIEF-IS = International Index of Erectile Function intercourse satisfaction domain; IIEF-OF = International Index of Erectile Function orgasmic function domain; IIEF-OS = International Index of Erectile Function overall satisfaction domain; IIEF-SD = International Index of Erectile Function sexual desire domain; ODF = oro-dispersible film.

treatment response. All patients presented normal ultrasound duplex findings (blood flow > 30 cm/second, end-diastolic velocity < 3 cm/second, resistance index > 0.8).

Table 2 presents mean changes of IIEF sub-scores from baseline to washout to final follow-up. Specifically, all IIEF sub-scores significantly decreased after the sildenafil washout period and significantly increased after use of the ODF formulation. For the comparison between sildenafil 100-mg FCT and sildenafil 75-mg ODF, we found significant differences in favor of sildenafil 100-mg FCT for IIEF-EF, IIEF-OF, IIEF-SD, and IIEF-IS and differences in favor of sildenafil 75-mg ODF for IIEF-OS. Figure 2 shows the absolute value of IIEF sub-scores during the study protocol.

For change in HADS score, we did not find significant differences from baseline to the sildenafil 100-mg FCT washout (mean difference = 0.0; $P = 1.0$), whereas significant differences were observed from the sildenafil 100-mg FCT washout to the final follow-up (mean difference = −0.19; $P < .01$).

For the ODF formulation, median CGI-I score was 3.5 (interquartile range [IQR] = 2.5−4.5) and median PGI-I score was 3.0 (IQR = 2.0−4.0). Concerning the time of action of sildenafil 75-mg ODF, median mouth time and action time were 60.0 seconds (IQR = 30.0−120.0) and 20.0 minutes (IQR = 15.0−30.0), respectively. All patients completed the study. There were 116 treatment-emergent adverse events (83.5%), all related to the bad taste. For global impression, 119 patients (85.6%) stated they would take the new drug again and 124 (89.2%) would suggest the drug to other patients.

DISCUSSION

In recent decades, many drug-delivery systems, including films, gels, chewing gums, and drug-loaded micro- and nanoparticles, have been developed as alternatives to conventional dosage forms, with the aim of improving patient convenience, acceptability, and compliance. Orally disintegrating films are much more convenient than the "old" oral tablet, because they are easily portable, do not need water to be taken, and can bypass the swallowing issues that some patients might experience. In fact, with this formulation, it would be sufficient to place it in the mouth and await its complete dissolution. It also is convenient for patients who have restrictions on daily fluid intake, such as those with decreased kidney function, congestive heart failure, and adrenal gland or endocrine system disorders. Ideally, the perfect drug-carrying film should be non-irritating, nontoxic, easily dissolved, and tasteless.

The median action time of sildenafil ODF in this study was 20 minutes; therefore, it has a greater rapidity of absorption, which can be attributed to its pre-gastric absorption.

In this study, the sildenafil ODF, hydrated by saliva when placed into the oral cavity, dissolved in approximately 1 minute. As expected, the only side effects recorded were related to bad taste, possibly because all patients had been using sildenafil 100-mg FCTs, which a priori excluded all patients who had previously suspended PDE5i therapy because of other side effects. Nevertheless, we can safely state that the new formulation of sildenafil 75 mg does not add any side effects to the "old" FCT formulation. Further studies in drug-naïve patients should be conducted to address the extent and frequency of side effects.

Furthermore, although more than 80% of patients expressed their concerns about the taste of this new formulation when dissolved in the mouth, almost 90% stated that they would recommend the drug to other patients, which reflects the excellent feedback reported. An important aspect that needs to be evaluated is the psychological aspect of patients taking sildenafil in this new formulation. Specifically, the ODF formulation could massively improve the quality of sexual life and psychological well-being of patients with ED because of its rapidity of action and ease of administration and because as it does not require water, glasses, or other objects necessary to take a tablet. This might explain why, despite the IIEF-EF, IIEF-OF, IIEF-SD, and IIEF-IS domain scores in favor of sildenafil 100-mg FCT, almost all patients stated they would recommend this new formulation. If so, then andrologists should approach ED treatments differently. The limitations of the study are related to the methodology used, because this was not a case-control study and the patients were not drug-naïve to ED treatment. For this reason, this article reports only the side effects related to the ODF but does not mention other side effects. This is obviously due to the selection of our patients, who were accustomed to treatment with sildenafil and might not have reported the typical side effects of PDE5i. In the future, a study on drug-naïve patients might provide a better understanding of the side effects.

In the production process for this film, the drug is evenly placed on the entire surface of the film.[14] Thus, by geometrically dividing this sheet of oral film exactly in the middle, one would be certain that the patient is taking exactly half the dosage. This might be useful in the common medical practice of advising the patient to take only part of the dosage when the effects of the full dosage are excessive.

CONCLUSIONS

The new ODF formulation is efficient and safe and does not add any side effect compared with the conventional FCT formulation. The introduction of a new sildenafil ODF provides a new option to the specialist for more precise tailored therapy.

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Conflicts of Interest: The authors report no conflicts of interest.

Funding: None.

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