The Efficacy and Safety of On-Demand Elonza; A Generic Product of Sildenafil in Thai Men with Erectile Dysfunction

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Objective: *To evaluate the efficacy and safety of Elonza® (generic product of sildenafil) 100 mg, a phosphodiesterase type 5 (PDE5) inhibitor, in Thai men with erectile dysfunction (ED).*
Material and Method: *This prospective, Cohort study was conducted for eight weeks. Two hundred ten male patients, older than 20 years of age with ED were enrolled to receive generic product of sildenafil 100 mg taken as needed. Efficacy is evaluated through the International Index of Erectile Function (IIEF) scores for the five separate response domains, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction domain.*
Results: *After sildenafil administration, erectile function domain scores were significantly increased from baseline, 5.02 ($p<0.001$) and 7.19 ($p<0.001$) in one month and two months, respectively. Intercourse satisfaction domain scores and overall satisfaction domain scores were significantly increased from baseline, 3.17 ($p<0.001$) and 1.74 ($p<0.001$) in two months, respectively. Most treatment emergent adverse events were mild or moderate. The most frequent treatment-emergent adverse events were flushing (13.2%), nasal congestion (9.8%), abnormal vision (4.9%), headache (4.4%), dizziness (2.9%), and dyspepsia (0.5%)*
Conclusion: *Elonza®, a generic product of sildenafil, was an effective and well-tolerated treatment for ED in Thai men.*

Keywords: *Sildenafil, Erectile dysfunction, International index of erectile function*

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Erectile dysfunction (ED), deemed as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance[1], is now recognized as a common condition[2]. Erectile dysfunction (ED) is a globally prevalent condition, having detrimental effects on overall quality of life, and providing a considerable source of emotional stress for men and their partners[3-6]. A variety of medical, psychological and lifestyle factors have been implicated in the etiology of erectile dysfunction (ED)[7-10]. This condition affects more than 150 million men across the world. The largest projected increases were in the developing world, i.e., Africa, Asia, and South America[11-13]. Results of one recent global projection suggested that as many as 322 million men would experience ED by 2025[12]. Erectile dysfunction is a chronic disease; however, therapy is currently administered as needed with oral phosphodiesterase 5 (PDE5) inhibitors[14]. Sildenafil is a popular drug used for improving penile erectile function that has been commercially available through several manufacturers and distributors in Thailand. It has been registered with US-FDA since 1998. This drug selectively inhibits enzyme cyclic GMP phosphodiesterase type 5 (cGMP PDE5) which is chiefly responsible for metabolism of cGMP in penile corpus carvernosum, leaving a high level of cGMP in penis[15].

Despite the high price of the drug from the innovator, sildenafil has been clinically used worldwide including Thailand since its launching. Recently, some generic sildenafil formulations are locally produced at lower price. In 2008, Kanjanawart et al[16] from Khon Kaen university reported the 100 mg sildenafil formulation of Elonza® is bioequivalent to the sildenafil reference of Viagra® in healthy Thai men (comparison of the peak plasma concentrations (Cmax) and area under the curve of concentration-time profile). The original test formulation was previously named as Erec® and changed to be Elonza® in 2007. Nevertheless, to ensure the efficacy and safety of these generic

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formulations, it is necessary to study the efficacy in men with erectile dysfunction. In the present study, the authors will demonstrate the efficacy and safety of on-demand sildenafil (100 mg).

Material and Method

Study design

This prospective, cohort study design, conducted between October 2010 and December 2011, assessed the efficacy and safety of sildenafil (100 mg) for the treatment of ED in Thai men. All patients provided written, informed consent. The present study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, and the principles of the Declaration of Helsinki.

Patients

Male patients more than 20 years of age with an International Index of Erectile Function-Erectile Function domain (IIEF-EF) score ≤25[17] were enrolled. Patients were required to have been with a stable sexual partner or in a stable relationship with a partner for more than six months.

Exclusion criteria were any unstable medical, psychiatric, or substance abuse disorder that was likely to affect the patient's ability to complete the study, presence of significant penile anatomical abnormalities (e.g. penile fibrosis or Peyronie's disease), spinal cord injury, ED caused by other sexual or endocrine disorders such as premature ejaculation, history of radical prostatectomy or other pelvic surgery with subsequent ED, clinically significant hepatobiliary or renal disease, poorly controlled diabetes (hemoglobin A1c >13%), unstable cardiovascular diseases (unstable or refractory angina, a recent history of myocardial infarction, certain arrhythmias, or uncontrolled hypertension), history of retinitis pigmentosa, the following medications were contraindicated, any drugs for the treatment of ED including PDE5 inhibitors, anticoagulants (except antiplatelet agents), androgens or antiandrogens, nitrates or nitric oxide donor medications, cytochrome P450 3A4 inhibitors, and alpha blocking agents.

Study medication

After a 4-week treatment-free run-in period, during which demographic information will be collected and physical examinations performed, eligible patients received a 2-month treatment with on-demand sildenafil regimens. Patients were given four sildenafil tablets per month (100 mg/tablet) for on-demand administration. The total of the population were 210 patients. Patients were instructed to self-administer treatment as needed before sexual intercourse, and to take the study medication 30 minutes to one hour before sexual intercourse, with a maximum of one dose daily. Dosage adjustments were not permitted in these studies.

Efficacy and safety assessments

Efficacy

Efficacy variable is the difference in change in International Index of Erectile Function-Erectile Function domain (IIEF-EF) score from baseline to end of washout.

Efficacy was also evaluated through the scores for the five separate response domains of male sexual function of the IIEF, erectile function (questions 1 to 5 and 15; total score, 1 to 30), orgasmic function (questions 9 and 10; total score, 0 to 10), sexual desire (questions 11 and 12; total score, 2 to 10), intercourse satisfaction (questions 6 to 8; total score, 0 to 15), and overall satisfaction (questions 13 and 14; total score, 2 to 10)[18]. The final score of each domain is the sum of scores for individual questions in that domain (with higher scores representing better sexual function).

Safety

A complete medical history, clinical laboratory tests, and a physical examination were conducted at both the first and the final visits. During the study, adverse events were collected at each visit. The investigator recorded the severity of the adverse events and their relationship to the study drug. Adverse events observed by the investigators. In addition, concomitant medication use was recorded, and blood pressure and heart rate were measured at each visit.

Statistical analysis

Analyses were conducted on an intent-to-treat basis. Efficacy analyses included all patients who had a baseline and two post-baseline measurements. Safety analyses included all randomized patients. The IIEF-15 scores were analyzed for the five IIEF domain scores, erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. SPSS® 11.5 was used for statistical analysis. Repeated measures ANOVA was used to evaluate changes in patient clinical IIEF-15 scores. P-value was considered as less than 0.05 for statistical significance.

Results

Demographic and baseline characteristics are shown in Table 1. Two hundred ten patients were enrolled. Only five discontinuations occurred. Two patients were lost to follow up, adverse events in two patients, and no effect of drug on one patient. Final populations in the present study were 205 patients. The mean age (range) of the patients was 59 (33-80) years. Mean weight was 70.7 kilograms. Mean BMI was 25.1. The patients had at least one of the three most commonly reported comorbidities - diabetes mellitus (14.6%), hypertension (20%), and dyslipidemia (37.6%).

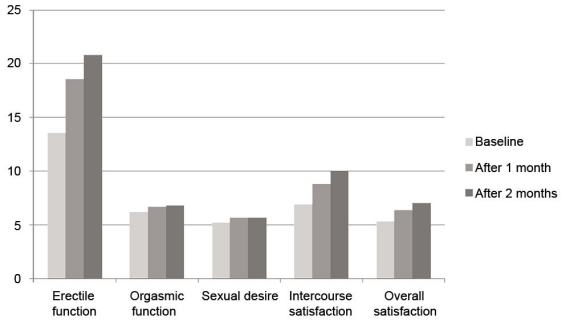

Fig. 1 Comparison of scores in the different domains of IIEF.

Efficacy results

The results of the present study (Table 2) showed that baseline of erectile function domain scores (range, 1-30) were 13.65±5.20 (mean ± SD). After sildenafil administration for one month, erectile function domain scores were 18.68±6.05 (5.02 or 36.7% increased from baseline; p<0.001). After sildenafil administration for two months, erectile function domain scores were 20.84±5.72 (7.19 or 52.9% increased from baseline; p<0.001) (Fig. 1).

For the baseline orgasmic function domain scores (range, 0-10), Baseline scores were 6.19±2.75. After one month of sildenafil administration, orgasmic function domain scores were 6.73±2.52 (0.54 or 8.0% increased from baseline; p<0.001). After two month of sildenafil administration, orgasmic function domain scores were 6.80±2.49 (0.61 or 9.7% increased from baseline; p<0.001).

Baseline for sexual desire domain scores (range, 2-10) were 5.21±2.25. After one month and two months of sildenafil administration, the sexual desire domain scores were increased to 5.75±2.13 (0.54 or 9.6% increased from baseline; p<0.001) and 5.74±2.02 (0.53 or 9.6% increased from baseline; p<0.001), respectively.

While baseline of intercourse satisfaction domain scores (range, 0-15) were 6.92±3.33. The results of intercourse satisfaction domain scores after one month and two months of sildenafil administration were 8.77±2.82 (1.85 or 27.5% increased from baseline; p<0.001) and 10.09±2.86 (3.17 or 44.9% increased from baseline; p<0.001), respectively.

In addition, when focus on the overall satisfaction domain scores, baseline scores (range, 0-15) were 5.30±1.98. The overall satisfaction domain scores were 6.37±1.73 (1.06 or 20.7% increased from baseline; p<0.001) in one month after sildenafil administration and 7.04±1.76 (1.74 or 32.8% increased from baseline; p<0.001) after two months of sildenafil administration.

Table 1. Patient demographics and baseline characteristics

Characteristic	Mean (range)
Age	59.0 (33-80)
Weight	70.7 (50-102)
BMI	25.1 (19.0-36.7)
Medical history	n (%)
Diabetes mellitus	30 (14.6%)
Hypertension	41 (20.0%)
Dyslipidemia	77 (37.6%)

Table 2. Effects of Sildenafil therapy on IIEF domains

IIEF domain	Baseline (mean ± SD)	After 1 month	Change from baseline	After 2 months	Change from baseline	p-value
Erectile function	13.65±5.20	18.68±6.05	36.7%	20.84±5.72	52.9%	<0.001
Orgasmic function	6.19±2.75	6.73±2.52	8.0%	6.80±2.49	9.7%	<0.001
Sexual desire	5.21±2.25	5.75±2.13	9.6%	5.74±2.02	9.6%	<0.001
Intercourse satisfaction	6.92±3.33	8.77±2.82	27.5%	10.09±2.86	44.9%	<0.001
Overall satisfaction	5.30±1.98	6.37±1.73	20.7%	7.04±1.76	32.8%	<0.001

Table 3. Adverse events

Adverse events	n (%)
Flushing	27 (13.2%)
Nasal congestion	20 (9.8%)
Abnormal vision	10 (4.9%)
Headache	9 (4.4%)
Dizziness	6 (2.9%)
Dyspepsia	1 (0.5%)

Safety results

Some patients experienced treatment-emergent adverse events. The most frequent treatment-emergent adverse events was flushing (13.2%), nasal congestion (9.8%), abnormal vision (4.9%), headache (4.4%), dizziness (2.9%), and dyspepsia (0.5%) (Table 3).

However, the majority of adverse events were of mild intensity and transient, resolving spontaneously by the end of the observation period. Two patients (0.98%) discontinued from the study (because of headache and dizziness).

Discussion

Since sildenafil was approved for marketing by the US Food and Drug Administration in March 1998, it has become the drug of choice for most men with ED[19].

In 2008, Kanjanawart et al[16] from Khon Kaen University reported the 100 mg generic formulation (Elonza®) was bioequivalent to the sildenafil reference product (Viagra®) in healthy Thai men. Nevertheless, to ensure the efficacy and safety of these generic formulations, it is necessary to study the efficacy in men with erectile dysfunction. In the present study, the authors will demonstrate the efficacy and safety of on-demand sildenafil (100 mg).

The five domains of the IIEF are currently considered validated tools for evaluation of ED[17].

Irwin Goldstein et al, 1998[23] reported that after 12-weeks treatment of sildenafil, the mean score for the erectile-function domain in the dose-escalation study was significantly higher for the men taking sildenafil (22.1) than for those taking a placebo (12.2, $p<0.001$).

The mean scores for the orgasmic-function, intercourse-satisfaction, and overall-satisfaction domains were also significantly higher in the sildenafil group ($p<0.001$), whereas the mean scores for sexual desire were not significantly different in the two groups ($p<0.13$).

Several studies showed that sildenafil had significant effects on erectile function, intercourse satisfaction, and overall satisfaction. There was no difference in sexual desire and orgasmic function[20-22]. Gomez F et al, 2002[20] reported that after 12-weeks treatment of sildenafil, mean final scores on erectile function, intercourse satisfaction, and overall satisfaction were significantly higher in the sildenafil group than they were in the placebo group. There were no differences between treatment groups on the orgasmic function and sexual desire domains. Marks LS et al, 1999[21] reported that after the 4- to 6-week period of sildenafil, mean IIEF scores at the follow-up visit were significantly greater than those at the baseline visit for all domains (all $p<0.01$). The greatest improvement from baseline was demonstrated in the domain comprising erectile function (66%), and the least improvement was in sexual desire (13%). Heiman JR et al, 2007[22] reported that after 12-weeks treatment of sildenafil, the IIEF domains of erectile function, intercourse satisfaction, and overall satisfaction ($p<0.001$ for all comparisons), but not orgasmic function or sexual desire.

The results of the present study were similar to these studies, after sildenafil administration, erectile function domain scores were significantly increased 52.9% from baseline in two months. Intercourse satisfaction domain scores and overall satisfaction domain scores were significantly increased from baseline, 44.9%, and 32.8% in two months, respectively. However, orgasm function and sexual desire function were slightly increased, 9.7% and 9.6%, respectively.

In other studies, sildenafil has not shown a significant effect on sexual desire. In contrast, there has been a significant effect on orgasmic function in most of the other reported studies.

For the placebo effect that could be found in some cases, from the study of Choi HK et al, 2003[24] that represent the efficacy of sildenafil in Asian populations, showed mean difference of IIEF-Erectile function domain score from baseline was 1.48 (11.4%) while previous studies from US[22] showed mean difference of IIEF-Erectile function domain score was 3.4 (27.0%). The results of previous studies published may represent that the placebo effect in Asian populations were lower than in US populations. Regarding the results reported in Asian populations that showed mean difference of IIEF-Erectile function domain score from baseline was 11.4%, which is quite low and showed significant lower than the treatment group. In our study, we also agree with the results from

previous reports that placebo effect could occur but will not interfere with the result of the present study.

For the adverse events of Elonza in the current study, the results showed flushing is the most common adverse events, followed by nasal congestion, abnormal vision, headache, dizziness, and dyspepsia. However, the majority of patients it was mild intensity, transient and can resolve spontaneously. When compared to other previous studies[20-24]. Heiman JR et al, 2007[23] reported the adverse events were found in 21% of patients, most of them had mild to moderate intensity reactions which was headache followed by vasodilatation, rhinitis, dyspepsia, and abnormal vision, respectively. While Gomez F et al, 2002[20] also reported the adverse events in half of the patients (51.3%) of which headache was the most common, followed by vasodilatation and dyspepsia, respectively. The adverse effect in the current study was similar to the previous studies published to date. Therefore, the current study had given the emphasis that sidenafil are well tolerance in the majority of patients.

Results indicate that Elonza® is safe and effective for the treatment of patients with ED similar to previous studies that were mentioned before[20-23].

A previous study[16] reported that bioequivalent of Elonza® was equal to the sildenafil reference product (Viagra®) in healthy Thai men. According to this similarity, in the present study the authors aimed to study in one arm, which have no placebo group. However, further studies may focus in the larger population and compare with the placebo group.

Conclusion

This study demonstrates that Elonza®, a generic product of sildenafil, is an effective and well-tolerated oral treatment for Thai men with ED. Sildenafil improves erectile function, intercourse satisfaction, and overall satisfaction.

Potential conflicts of interest

None.

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การศึกษาประสิทธิภาพและความปลอดภัยของการใช้ยาซิลเดนาฟิล [Sildenafil (Elonza®)] ขนาด 100 มิลลิกรัม ในผู้ป่วยชายไทยที่มีอาการหย่อนสมรรถภาพทางเพศ

อุดมศักดิ์ วิจิตรเศรษฐกุล, สมพล เพิ่มพงศ์โกศล

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและความปลอดภัยในการใช้ยาสามัญของซิลเดนาฟิล (Elonza®) ซึ่งยับยั้งเอนไซม์ฟอสโฟไดเอสเทอเรสชนิดที่ 5 ในชายไทยที่มีภาวะหย่อนสมรรถภาพทางเพศ*

ผู้ป่วยและวิธีการ: *เป็นการศึกษาแบบติดตามไปข้างหน้าเป็นเวลา 8 สัปดาห์ ในชายไทย 210 คน ที่มีภาวะหย่อนสมรรถภาพทางเพศที่มีอายุมากกว่า 20 ปี ถูกคัดเข้าสู่การศึกษา จะได้รับยาสามัญของซิลเดนาฟิล 100 มิลลิกรัม รับประทานเมื่อต้องการมีเพศสัมพันธ์ ประสิทธิภาพของยาประเมินโดยคะแนน IIEF-15 ซึ่งแยกเป็น 5 หัวข้อ: ด้านการแข็งตัวของอวัยวะเพศ, การถึงจุดสุดยอด, ความต้องการทางเพศ, ความพึงพอใจในการมีเพศสัมพันธ์ และความพึงพอใจโดยรวม*

ผลการศึกษา: *หลังจากได้รับยาสามัญของซิลเดนาฟิล ด้านการแข็งตัวของอวัยวะเพศเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ โดยเพิ่มขึ้น 5.02 คะแนน และ 7.19 คะแนน ในระยะเวลา 1 และ 2 เดือนตามลำดับ ด้านความพึงพอใจในการมีเพศสัมพันธ์ และความพึงพอใจโดยรวม เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ โดยเพิ่มขึ้น 3.17 คะแนน และ 1.74 คะแนน ในสองเดือนตามลำดับ ผลข้างเคียงจากยาส่วนใหญ่คือ หน้าแดง (13.2%) คัดจมูก (9.8%) การมองเห็นผิดปกติ (4.9%) ปวดศีรษะ (4.4%) วิงเวียน (2.9%) และปวดท้อง (0.5%)*

สรุป: *ยาสามัญของซิลเดนาฟิล มีประสิทธิภาพและปลอดภัย ต่อการรักษาภาวะหย่อนสมรรถภาพทางเพศในชายไทย*