



Mirodenafil for the Treatment of Erectile Dysfunction: A Systematic Review of the Literature

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Phosphodiesterase type 5 (PDE5) inhibitors are the most commonly used treatment for erectile dysfunction (ED). Since the launch of sildenafil, several drugs – including mirodenafil, sildenafil citrate (sildenafil), tadalafil, vardenafil HCL (vardenafil), udenafil, and avanafil – have become available. Mirodenafil is a newly developed pyrrolopyrimidinone compound, which is a potent, reversible, and selective oral PDE5 inhibitor. Mirodenafil was launched in Korea in 2007, and an orally disintegrating film of mirodenafil was developed in 2011 for benefitting patients having difficulty in swallowing tablets. This study aimed to review the pharmacokinetic characteristic profile of mirodenafil and report evidence on its efficacy in the case of ED. In addition, we reviewed randomized controlled studies of mirodenafil's daily administration and efficacy for lower urinary tract symptoms.

Key Words: Erectile dysfunction; Phosphodiesterase 5 inhibitors; Review; Treatment efficacy

INTRODUCTION

Phosphodiesterase type 5 (PDE5) inhibitors are the most commonly used drugs to treat erectile dysfunction (ED). Since the launch of sildenafil, several compounds – including mirodenafil, sildenafil citrate (sildenafil), tadalafil, vardenafil HCL (vardenafil), udenafil, and avanafil – have become available. These PDE5 inhibitors are taken prior to anticipated sexual activity and have been proven efficacious and well tolerated. Mirodenafil is a newly developed pyrrolopyrimidinone compound; it is a potent, reversible,

and selective oral PDE5 inhibitor [1,2]. Mirodenafil was launched in Korea in 2007, and an orally disintegrating film of mirodenafil was developed in 2011 for benefitting patients having difficulty in swallowing tablets.

The T_{max} and $t_{1/2}$ values of mirodenafil are 1.25 and 2.5 hours, respectively. Preclinical studies have revealed that the selectivity of mirodenafil toward PDE5 is 10-fold higher than that of sildenafil, but the inhibitory effects of mirodenafil on other PDEs are lower than those of sildenafil [3]. One study showed that mirodenafil significantly improves ED and is well tolerated in a representative pop-

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ulation of Korean males with broad-spectrum ED of various etiologies and severities [1]. A new trend has developed in the field of sexual medicine, particularly regarding PDE5 inhibitor medication. Daily administration of PDE5 inhibitors is useful for a proportion of ED patients. In addition, the beneficial effects of PDE5 inhibitors on lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) have been demonstrated in several clinical trials. This study aimed to review the pharmacokinetic characteristic profile of mirodenafil and report evidence on its efficacy for ED. In addition, we reviewed randomized controlled studies of daily administration and efficacy of mirodenafil for LUTS.

PHARMACOKINETICS OF MIRODENAFIL

Mirodenafil (5-ethyl-2-(3-7-propyl-3,5-dihydropyrrolo [3,2-d]pyrimidin-4-one) is a novel pyrrolopyrimidinone compound and a reversible PDE5 inhibitor. Mirodenafil has a molecular weight of 531.25 Da. It is modified from sildenafil at the N- or O-side chain and has a dihydropyrrole ring instead of a pyrazole ring [4].

After oral administration of ^{14}C -mirodenafil (40 mg/kg) to rats, 0.98% and 82.92% of the administered radioactivity for the first 24-hour period was recovered from their urine and feces, respectively. The total radioactivity recovered within 7 days was 92.32%, with 91.25% and 1.07% excreted in the feces and urine, respectively, indicating that the absolute gastrointestinal absorption rate is at least 92% [3]. The plasma concentration reached its maximum value (C_{\max}) of 4,773 ng/mL at 1.7 hours after dosing in rats and decreased with a half-life ($t_{1/2}$) of 4.0 hours. The corpus cavernosum concentration reached a C_{\max} of 2,812 ng/mL at 1.4 hours after dosing in rats and decreased with a $t_{1/2}$ of 1.3 hours. After oral administration of mirodenafil (100 mg) in humans, the C_{\max} was 354.9 ng/mL at 1.0 hour and decreased with a $t_{1/2}$ of 1.6 hours [5-7].

Although mirodenafil is completely absorbed following oral administration, its mean absolute bioavailability is relatively low. Oral bioavailabilities based on total radioactivity are estimated to be 60.4%, 62.2%, and 69.9% for 10, 20, and 40 mg/kg doses in rats, respectively. The oral bioavailabilities of parent mirodenafil have been estimated to be 24.1%, 30.1%, and 43.4% for 10, 20, and 40

mg/kg doses in rats, respectively [5], which resulted from extensive first-pass metabolism. After oral administration of mirodenafil (20 mg/kg), ~2.59% of the oral dose is not absorbed, and the hepatic and gastrointestinal first-pass effects of mirodenafil are ~21.4% and ~54.3% of the oral dose, respectively [8].

After oral administration of a 40 mg/kg dose of ^{14}C -mirodenafil in rats, radioactivity is distributed in all tissues. The tissue/plasma radioactivity ratio at 1 hour after administration is 0.5 to 2.6, with the exception of the excretory organs [5]. The highest radioactivity concentrations are found in the gastrointestinal tract. Radioactivity levels in most tissues decrease with time, and elimination is almost complete within 24 hours. However, radioactivity remains detectable with a relatively high penetration in the thyroid, liver, and brain of rats [5,8]. Radioactivity in the brain increases gradually with time up to 24 hours post dose because it seems that ^{14}C -mirodenafil crosses the blood-brain barrier and inhibits PDE5 in the cerebral blood vessels. The binding ratios of mirodenafil to plasma proteins in rats are >97% *in vitro* and >98% *in vivo* [5,8].

The pharmacokinetics of mirodenafil after oral administration (10, 20, and 50 mg/kg) to rats is dose-dependent due to saturable hepatic metabolism. The changes in C_{\max} and area under the plasma concentration-time curve (AUC) across the 10 to 50 mg/kg range show a linear dependence on dose escalation. The T_{\max} value is 30 minutes, and the $t_{1/2}$ value is 30.5 to 41.3 minutes at all doses [8].

Mirodenafil undergoes extensive biotransformation in human liver microsomes with 10 metabolites formed mainly due to breakdown via cytochrome P450 (CYP3A4) in addition to minor contributions by CYP2C. Mirodenafil inhibits CYP3A4, CYP2C19, and CYP2D6 activities with IC50 values of 15.6, 38.2, and 77.0 μM , respectively. Mirodenafil metabolites have a 10-fold lower *in vitro* potency for PDE5 inhibition compared with that of mirodenafil [9].

Biliary excretion of radioactivity during the first 24 hours is ~38.82%, and the hepatobiliary system serves as the main route of excretion for mirodenafil and its metabolites after both oral and intravenous administration. The excretion of mirodenafil and its metabolites is almost complete after 7 days post oral administration in rats (91.2%).

The main route of excretion is through feces (>91% of dose) via bile after oral dosing [3,5,8].

ANIMAL STUDIES

The pharmacokinetic properties of mirodenafil have been compared with those of sildenafil in rats. After oral administration of both mirodenafil (40 mg/kg) and sildenafil (40 mg/kg), plasma concentrations reached C_{max} values of 2,728 ng/mL at 1.0 hour and 173 ng/mL at 1.6 hours after dosing in rats and decreased with a $t_{1/2}$ of 1.5 and 1.4 hours, respectively. The corpus cavernosum concentration reached a C_{max} of 2,812 ng/mL at 1.4 hours and 1,116 ng/mL at 1.4 hours after dosing in rats and decreased with a $t_{1/2}$ of 1.3 and 0.9 hours. The C_{max} and AUC of mirodenafil were significantly higher than those of sildenafil in the plasma and corpus cavernosum tissue [6].

The effect of mirodenafil on tissue relaxation in a rabbit model organ bath study demonstrated that the corpus cavernosum relaxes in response to mirodenafil in a dose-dependent manner. Additionally, the relaxation effects of mirodenafil increase when rabbits are pre-treated with *Ginkgo biloba* extract (vasorelaxive effects are the main function) [10].

In a spinal cord injury rabbit model, mirodenafil or sildenafil produces a penile erection response. The onset of erectile activity with mirodenafil is quicker than that with sildenafil citrate [11]. The effects of chronic mirodenafil administration on the facilitation of pelvic nerve-mediated penile erection in a diabetic ED rat model and a cavernosal nerve injury ED rat model demonstrate that chronic mirodenafil treatment has a significant effect on increasing intracavernosal pressure [12,13]. Chronic treatment with mirodenafil enhances erectile function in an ED animal model.

PHARMACOLOGICAL PROFILE OF MIRODENAFIL COMPARED WITH OTHER PHOSPHODIESTERASE TYPE 5 INHIBITORS

The T_{max} and $t_{1/2}$ values for mirodenafil are 1.25 and 2.5 hours, respectively [1]. As summarized in Table 1 [14-19], the T_{max} value is similar to that of sildenafil, and the $t_{1/2}$ value is shorter than that of any other drug listed in Table 1. However, no head-to-head comparative study has been conducted. The pharmacokinetics of mirodenafil is not affected by alcohol, which is similar to other traditional PDE5 inhibitors (sildenafil, vardenafil, and tadalafil) [20,21]. Fatty food intake affects the pharmacokinetic profiles of sildenafil and vardenafil but not that of tadalafil [18,19,22]. However, scant data are available on the effect of food on mirodenafil pharmacodynamics. Thus, further studies are needed to elucidate their relationships.

CLINICAL TRIALS REVIEW: EFFICACY AND SAFETY OF MIRODENAFIL

1. Broad population of males with erectile dysfunction

The first clinical data concerning the efficacy of mirodenafil were reported in 2008 [1]. That multicenter, randomized, double-blind, placebo-controlled study was performed after a 4-week run-in baseline period during which no drug or placebo was offered. Patients were prescribed mirodenafil at fixed doses of 50 or 100 mg for 12 weeks on an 'as-needed' basis. The mean age of all subjects was 52.9 years. At baseline, 3.2% of all subjects had mild ED (scores of 22 ~ 25), 29.7% had mild-to-moderate ED (scores of 17 ~ 21), 43.2% had moderate ED (scores of 11 ~ 16), and 23.9% had severe ED (scores of 1 ~ 10). Finally, 215 (96.4%) of the 223 males completed the trial. The primary outcome measure (International Index of

Table 1. Pharmacokinetics of mirodenafil and three traditional phosphodiesterase type 5 inhibitors (tadalafil, sildenafil, and vardenafil)

	Mirodenafil 100 mg	Sildenafil 100 mg	Tadalafil 20 mg	Vardenafil 20 mg
T_{max} (h)	1.25	0.83 ~ 1.2	2.0	0.7 ~ 1.0
$T_{1/2}$ (h)	2.5	3.7 ~ 3.8	17.5	3.3 ~ 3.9
C_{max} (ng/mL)	373.4	327	378	20.9

T_{max} : time of maximum drug concentration, $T_{1/2}$: half-life of the drug, C_{max} : maximum drug concentration.

Erectile Function [IIEF] question [Q] 3 score) increased by 0.68 from the baseline in the placebo group compared with 1.16 and 1.64 in the mirodenafil 50- and 100-mg groups, respectively. The IIEF Q3 scores of the mirodenafil 50- and 100-mg groups increased by a significantly greater amount than those of the placebo group ($p=0.0001$ and $p<0.0001$, respectively).

These results are comparable with those of other PDE5 inhibitors, although no head-to-head comparative studies have been conducted. In the first clinical trial of sildenafil involving males with ED, the IIEF Q3 score increased by 0.1 from the baseline in the placebo group compared with increases of 1.6 and 2.0 in the sildenafil 50- and 100-mg groups, respectively [23]. In the initial results of tadalafil in 179 males with ED (8.9% had mild ED, 37.6% had mild-to-moderate ED, 28.7% had moderate ED, and 24.8% had severe ED), the IIEF Q3 score increased by 0.3 from the baseline in the placebo group compared with increases of 1.0 and 1.3 in the 10- and 25-mg dose groups, respectively [24]. In the first clinical trial of vardenafil involving 580 males with ED (37.5% had moderate ED and 31.9% had severe ED), the IIEF Q3 score increased by 0.2 from the baseline in the placebo group compared with increases of 1.3 and 1.5 in the vardenafil 10- and 20-mg groups, respectively.

A recent meta-analysis reported no major differences in efficacy among the three traditional PDE5 inhibitors (tadalafil, sildenafil, and vardenafil), but further studies of other PDE5 inhibitors (avanafil, lodenafil, udenafil, and mirodenafil) and a comparison of efficacy among the various PDE5 inhibitors are needed because of limitations in the quality and quantity of the currently available evidence [25].

2. Erectile dysfunction patients with chronic disease

The findings from many epidemiological studies show

that ED is associated with chronic diseases such as diabetes mellitus (DM), hypertension, and spinal cord injury [26]. Several studies have shown that PDE5 inhibitors improve ED in males with chronic diseases [27-30]. However, few studies have been conducted on mirodenafil in this regard despite the general presumption that mirodenafil is also effective for ED in subjects with chronic diseases.

In a study of the pharmacokinetics of mirodenafil in streptozotocin-induced DM rats [31], mirodenafil was detected in the plasma in 5 minutes and was absorbed with a T_{max} of 15 to 60 minutes in both the control and DM groups. The C_{max} and total area under the plasma concentration curve from time zero to infinity for mirodenafil in the DM group were also comparable to those in the control group. In a randomized, placebo-controlled clinical trial in patients with diabetes [32], the on-demand dosing of mirodenafil resulted in a significant improvement in erectile function (Table 2), and the drug was safe and well-tolerated irrespective of the baseline severity of DM. However, only a low dose of mirodenafil (50 mg) was used in this trial considering that the maximum dose of a PDE5 inhibitor is generally required in patients with DM [33].

In a study on the pharmacokinetics of mirodenafil in hypertensive rats [34], 16-week-old spontaneously hypertensive rats (SHRs) (an animal model of the chronic phase of essential hypertension) showed significantly greater intravenous AUC and comparable oral AUC of mirodenafil compared with those of the controls. The AUCs of intravenous and oral mirodenafil in 6-week-old SHRs were significantly greater than those in the controls. Additionally, the AUC of oral mirodenafil alone in 16-week-old deoxycorticosterone acetate salt-induced rats (an animal model of secondary hypertension) was significantly smaller than that in the control rats. These results suggest that the pharmacokinetics of mirodenafil may not be affected by essen-

Table 2. Comparison of efficacy parameters between mirodenafil and other phosphodiesterase type 5 inhibitors in patients with diabetes and erectile dysfunction [27,32,33]

Item		Mirodenafil	Sildenafil	Vardenafil	Tadalafil
IIEF EF domain	Change from baseline (score)	9.3	7.08	5.42	6.40
GAQ	Satisfaction (%)	77	56	72	64

IIEF EF domain: International Index of Erectile Function erectile function domain, GAQ: global assessment questionnaire.

tial hypertension itself. However, a more important clinical issue is the relationship between ED and hypertension, and the possible interaction between mirodenafil and antihypertensive drugs. In an experimental study of the effects combining mirodenafil with antihypertensive drugs on the relaxation of rabbits' corpus cavernosum [35], the effect of mirodenafil was significantly enhanced by an angiotensin receptor blocker (losartan), a calcium channel blocker (nifedipine or amlodipine), and an alpha adrenergic blocker (doxazosin or tamsulosin) by >40%, but not by an angiotensin-converting enzyme inhibitor. These results are comparable to those of other PDE5 inhibitors and suggest that mirodenafil, like other PDE5 inhibitors, should be initiated at a lower dose in patients using hypertensive drugs. In a randomized, placebo-controlled clinical trial in patients taking an antihypertensive drug [36], the on-demand dosing of mirodenafil resulted in a significant improvement in erectile function, and the efficacy of mirodenafil seemed to be comparable to that of other PDE5 inhibitors (Table 3). Furthermore, mirodenafil did not show clinically significant long-term changes in hypertension-associated parameters such as blood pressure, heart rate, or electrocardiographic findings. However, a relatively small percentage of patients taking diuretics (14.8%) and a beta adrenergic blocker (25.9%) were enrolled, and the immediate effects of mirodenafil on hypertension-associated parameters were not evaluated.

Several studies suggest that PDE5 inhibitors, particularly sildenafil, in patients with spinal cord injury are first-line therapy for ED [30]. However, it is difficult to distinguish among the PDE5 inhibitors and to counsel individual patients in clinical practice. Only one experimental study on

mirodenafil is available in this area. In an acute spinal cord-injured rabbit model, mirodenafil significantly improved erectile function, and its efficacy was greater than that of sildenafil with respect to the peak length of the penile mucosa and the onset time of action [11].

A study of the use of mirodenafil combined with dapoxetine in patients with premature ejaculation (PE) without ED has been published [37]. Mirodenafil combined with dapoxetine showed better results in terms of intravaginal ejaculatory latency time and PE profile index score, and similar treatment-emergent adverse events, compared with those of dapoxetine alone. This was the first randomized, placebo-controlled clinical trial on the use of a PDE5 inhibitor combined with dapoxetine for PE. This result suggests that adding a PDE5 inhibitor to dapoxetine may be more effective and safer than dapoxetine alone.

The efficacy and tolerability of mirodenafil are expected to be comparable to or better than those of other PDE5 inhibitors in patients with ED and a chronic disease because mirodenafil demonstrates higher selectivity toward PDE5 and lower selectivity toward other PDE family members than sildenafil [3]. Moreover, experimental and clinical data show the usefulness of mirodenafil. However, there is insufficient evidence to demonstrate the usefulness of mirodenafil in patients with ED and a chronic disease. Further research is needed to answer this question.

3. Once daily mirodenafil treatment

Since 1998, when sildenafil came onto the market, PDE5 inhibitors have been used for ED as first-line treatment [23,38]. Many studies have reported the effectiveness and safety of the daily administration of PDE5 in-

Table 3. Comparison of efficacy parameters between mirodenafil and other phosphodiesterase type 5 inhibitors in patients with erectile dysfunction concomitantly taking antihypertensive drugs [36]

Item		Mirodenafil	Sildenafil	Vardenafil	Tadalafil
IIEF EF domain	Change from baseline (score)	9.4			9.4
IIEF Q3	Change from baseline (score)	1.4	1.5		
IIEF Q4	Change from baseline (score)	1.9	1.6		
SEP2	Change from baseline (%)	30		33	
SEP3	Change from baseline (%)	55		49	
GAQ	Satisfaction (%)	84	86	80	87

IIEF EF domain: International Index of Erectile Function erectile function domain, Q: questionnaire, SEP: sexual encounter profile, GAQ: global assessment questionnaire.

hibitors [39-42].

The rationale for daily administration of PDE5 inhibitors to treat ED is based on a report by Eardley et al [43] published in 2004. According to this report, people usually initiate sex within 30 minutes of their intention to do so irrespective of the presence of ED. Another study on females conducted by Fisher et al [44] in 2005 reported that 30% and 34%, respectively, of males and females have sexual intercourse without a schedule. These two studies confirm that the behavior and timing of sexual intercourse between males and females cannot be anticipated and explain the limitation of on-demand PDE5 inhibitor therapy, which needs to be administered prior to sexual intercourse. The unpredictable timing and short lead time for sex may be a rationale for the daily administration of PDE5 inhibitors.

Males with ED mostly want to be able to have sex any time with a spontaneous erection [45]. The ability to have a spontaneous erection is more important for them than sexual intercourse itself. Porst et al [46] reported that daily administration of a PDE5 inhibitor allows patients with ED to obtain spontaneous erections. Daily administration of a PDE5 inhibitor is meaningful because a patient can have spontaneous erections and perform intercourse without having to take a PDE5 inhibitor beforehand.

Daily administration of tadalafil is a method of obtaining a spontaneous erection in patients with ED and allowing them to forget about their disease [46]. The basis of the study was that through daily administration, agents with a comparatively long half-life could remain in the blood at a level higher than the minimally effective concentration. However, Chung et al [42] reported that once daily administration of mirodenafil, which has a T_{max} of 1.25 hours and a $t_{1/2}$ of 2.5 hours [2], improves the sexual function and LUTS of patients.

Konstantinopoulos et al [47] reported that a significant increase in ET-1, nitric oxide (NO), and cGMP is observed in patients with ED when the molecular markers (ET-1, NO, cGMP, thrombomodulin, E-selectin, and vEF) of the endothelial function affecting erectile function were measured after once daily treatment with sildenafil, which has a comparatively short half-life. As a result of animal experiments, the mirodenafil-administration group showed a larger AUC and a higher peak serum concentration of the therapeutic drug than the sildenafil-administration group [6]. As shown

in these two studies, the once daily treatment with mirodenafil is expected to improve endothelial function as well as the once daily treatment of sildenafil. Zhao et al [48] reported the efficacy of a once daily udenafil treatment in patients with ED. They found that the daily administration of 50 mg of udenafil had mild side effects and was effective in improving ED. In another study, Zhao et al [49] reported a difference between the blood and tissue concentrations after administering a PDE5 inhibitor prior to transurethral prostatectomy in patients with BPH. In animal experiments, concentrations of mirodenafil in the plasma and the corpus cavernosum were confirmed to be different [6]. On the basis of these results, the effects of the once daily treatment cannot be determined by using the blood concentration of the agent and half-life. A post-antibiotic effect—sub-minimum inhibitory concentration effect is observed in the cases of antibiotic agents. This is the mechanism of delayed cell growth, morphological changes, and increasing post-antibiotic effects even though the level of antibiotic in blood is lower than the minimal inhibitory concentration [50]. This result suggests that PDE5 inhibitors can affect the body at a level lower than the minimally effective concentration. In addition, a once daily treatment with agents having a short half-life can be effective due to pharmacodynamic factors such as drug distribution, bioavailability, and reabsorption [51].

4. Lower urinary tract symptom

The prevalence of both ED and LUTS associated with BPH increases with age. Clinical evidence shows that ED and LUTS due to BPH have a common pathophysiology [52]. The first-line treatment options for BPH-LUTS include pharmacotherapy with α_1 -adrenergic blockers or 5 α -reductase inhibitors. The latter are prescribed when there is significant prostatic enlargement. Both types of agents are associated with unwanted side effects, including orthostatic hypotension and dizziness with α_1 -adrenergic blockers, decreased libido and ED with 5 α -reductase inhibitors, and ED with both [53]. Additionally, α_1 -adrenergic blockers can cause anejaculation or retrograde ejaculation, whereas 5 α -reductase inhibitors can decrease ejaculate volume. Due to the limitations of current therapy, numerous clinical trials have been conducted to test the potential role of PDE5 inhibitors in BPH-LUTS treatment.

Although the exact mechanism of action remains to be clarified, PDE5 inhibitors have shown efficacy in treating LUTS in males with and without ED. These drugs may be considered first-line treatment for males with an ED history. With the advent of an additional class of drugs to treat LUTS, medical therapy can be individualized for ensuring maximum patient benefit. Three studies concerning the use of mirodenafil in LUTS are included in the current literature: two on the combination of mirodenafil with α_1 -blockers and one on mirodenafil vs. placebo. The first trial to examine the role of mirodenafil in the treatment of LUTS was a multicenter, open-label prospective study of 121 males with ED [54]. All patients were given α_1 -blockers (0.2 mg of tamsulosin or 10 mg of alfuzosin) to treat LUTS/BPH for >3 months before the study commenced, and the patients were then given two oral mirodenafil doses of 100 mg per week to be taken before intercourse. It was emphasized that the patients should take the mirodenafil at least 6 hours after having the α_1 -blocker. The participants completed the International Prostate Symptom Score (IPSS)/quality of life (QoL), peak urine flow rate (Q_{max}), post void residual volume (PVR), and IIEF-5 tests at baseline and again during 4- and 8-week reviews. After 8 weeks of treatment with mirodenafil, there were significant improvements in the IIEF-5 and the IPSS/QoL but not Q_{max} or PVR. Facial flushing was the most common adverse effect, followed by headache and dizziness. None of the subjects dropped out of the study because of adverse effects. The second study was a multicenter, open-label prospective study that assessed the clinical efficacy and safety of mirodenafil co-administered with an α_1 -blocker to patients with both BPH-LUTS and ED [55]. A total of 147 sexually active males with a history of BPH-LUTS and ED for ≥ 3 months were eligible. Apart from having a personal history of BPH-LUTS and ED, the patients enrolled in this trial had been receiving stable α_1 -blocker therapy for at least 4 weeks, although they were not fully satisfied with their current medical treatment. In addition to maintenance α_1 -blocker therapy, all patients were prescribed 50 mg of mirodenafil OD after enrollment. The co-primary measures were the IPSS and the IIEF-5, and the key secondary measures were Q_{max} and PVR volume at baseline and 8 weeks. The IIEF-5 score improved at 8 weeks. The combination of mirodenafil with a α_1 -blocker did not sig-

nificantly improve PVR; however, Q_{max} improved at 8 weeks. Hot flashes (10.9%) were the most common adverse effect, followed by headache (8.1%). The third was a multicenter, double-blind placebo-controlled trial involving 134 males with ED who were administered mirodenafil [42]. The patients were randomly allocated into two groups. Group 1 (90 patients) received 50 mg of mirodenafil once daily, and group 2 (90 patients) received a placebo daily. IIEF-5, IPSS, Q_{max} , and PVR were assessed at 4, 8, and 12 weeks after the start of treatment. Of the 180 patients, 71 in group 1 and 63 in group 2 completed the 12-week clinical trial. After 12 weeks of once daily 50 mg of mirodenafil administration, the group 1 patients showed significant improvements in the IIEF-5 scores compared with group 2 patients. Significant improvements in LUTS were observed in the IPSS/QoL and uroflowmetry across the treatment group as secondary efficacy variables compared with those in the placebo group. Headache was the most common adverse effect, followed by facial flushing. The results of three studies concerning the use of mirodenafil in patients with LUTS suggest that mirodenafil significantly improves LUTS and erectile function in males with BPH. Mirodenafil seems to be a treatment option for patients with LUTS secondary to BPH with ED. Further studies are needed to determine the long-term outcomes, and a large-scale study is required for further evaluation of efficacy.

CONCLUSIONS

Although mirodenafil shares its mechanism of action with other PDE5 inhibitors to improve ED, the potential benefit of mirodenafil compared with other PDE5 inhibitors is noteworthy. The efficacy of mirodenafil for treating patients with ED, those with combined diseases, and those with LUTS has been demonstrated in many well-designed, controlled trials. In addition, daily treatment with mirodenafil is a useful option with similar efficacy and safety as on-demand treatment.

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