A NEW APPROACH FOR THE PATIENT WITH ERECTILE DYSFUNCTION

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MEETING SUMMARY

This satellite symposium was held in two sessions. The first session was offered in a traditional format where invited experts reviewed and discussed the latest concepts and developments on the management of erectile dysfunction (ED). During the second session, experts discussed clinical cases from their real-life practice in an interactive format, to facilitate discussions with the audience, and to provide participants with the most relevant aspects of ED. The symposium objectives were to review and discuss the current status of the management of ED and treatment needs for patients with ED, and to explore the latest evidence on the use of topical alprostadil cream (Vitaros®, Virirec®, Vytaros®)[1] – who benefits the most?

Opening Remarks from the Chair

Doctor Ian Eardley

In 2013 alprostadil cream received a European marketing authorisation for the treatment of ED in men from the age of 18 years.[1] In the latest updates of the European Association of Urology (EAU) guidelines on male sexual dysfunction,[2] alprostadil cream is included as a new treatment option in the management of ED. Oral selective phosphodiesterase type-5 (PDE-5) inhibitors (e.g. avanafil, sildenafil, tadalafil, or vardenafil) are recommended as the first-line pharmacotherapy, assuming that there are no contraindications or drug interactions. Other treatments and/or forms of therapy can be considered in suitable patients. In this symposium, the use of alprostadil cream as an alternative and/or first-line treatment option for patients with ED is discussed.

Management of ED: Room for Improvement?

Professor Hartmut Porst

Prof Porst discussed the treatment options for ED and what patients' expectations of treatment are in the context of an important sexual life.

The landscape of ED worldwide

According to the latest statistics published by the Durex Network Research Unit for the years 2005–2009, sex remains an important part of our lives, although the frequency of sexual activities and the importance given to these varies widely across countries.[3] The highest prevalence was observed in Greece and Brazil where up to 80–87% of the population have sex at least once a week, followed by Russia and China (72–80%), and the UK and USA (34–55%). In contrast, less than 34% of the Japanese population reported having sex once a week.[3]

The landscape for sexual disorders in men shows no significant differences worldwide. The prevalence of sexual disorders, including ED, increases with age (Table 1). In a survey conducted to evaluate the sexuality and health among older adults in the USA,[4] the prevalence of ED was estimated to be 31% in men aged 57–64 years to up to 45% in men over the age of 65 years.[4] The survey also indicated that the majority of men aged 57-85 years and suffering from sexual disorders were bothered by these, with ED at the top of the ranking (90%) followed by the lack of libido (65%), premature ejaculation, and inability to climax (65–73%).[4] 'Bothersome' was defined in the degree of 'somewhat' or 'a lot' as rated by the responders in the range of 'a lot', 'somewhat', or 'not at all'.[4]

The severity of ED also increases with age.[2-5] Over 40% of men aged 70–79 years suffer from severe ED, while over 90% of younger men aged 40–49 years have either no ED or a mild-to-moderate dysfunction.[5]

The therapeutic landscape for ED

There is a large number of treatment options ranging from PDE-5 inhibitors to intracavernosal or intraurethral alprostadil (prostaglandin E_1 [PGE_1]), vacuum erection devices, hormone replacement therapy (testosterone), sexual counselling, and penile implants. The mode of action differs between therapeutic modalities (Figure 1). PDE-5 inhibitors block the cleavage of cyclic guanosine monophosphate (cGMP) via inhibition of the enzyme PDE-5.[6,7] Instead, alprostadil activates the cyclic adenosine monophosphate (cAMP) pathway. Alprostadil binds directly to the G-protein-coupled PGE_1 receptors on the smooth muscle cell surface, to convert adenosine triphosphate to cAMP. An enzyme cascade ultimately results in a reduction in the cytoplasmic Ca^{2+} available for smooth muscle contraction.[8] The intracavernous accumulation of cGMP or cAMP causes relaxation of the cavernous arteries and smooth muscle cells lining the blood vessels of the penis, ultimately resulting in an increase of arterial blood flow with enlargement of the cavernous bodies. This process impedes return of the venous blood and maintains erection.[6,7,9]

Table 1: Prevalence (%) of sexual disorders by age in adults in the USA.[4]

Age, years	Sexual disorder*		
	Premature ejaculation	Delayed/absent ejaculation/orgasm	ED
57–64	29.5 (23.4–35.7)	16.2 (11.9–20.5)	30.7 (25.3–36.0)
65–74	28.1 (23.4–32.9)	22.7 (17.5–27.9)	44.6 (38.7–50.5)
75–85	21.3 (13.2–29.3)	33.2 (25.0–41.5)	43.5 (34.5–52.4)

*Values represent prevalence % estimates (95% confidence intervals)
ED: erectile dysfunction.

Prescribing information can be found at the end of the article.

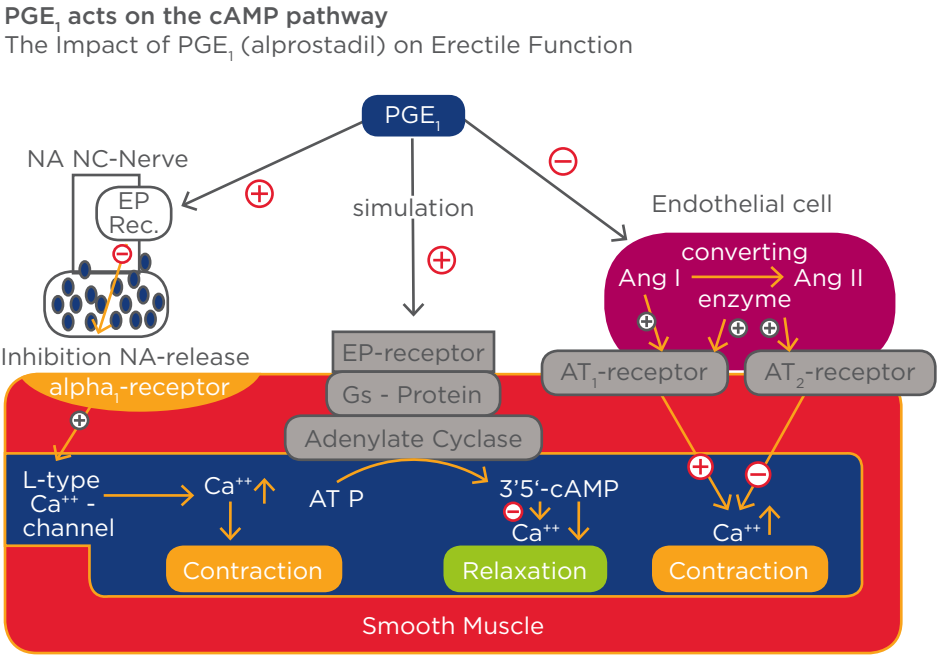

Figure 1: Mode of action of alprostadil (PGE_1) versus PDE-5 inhibitors.
cAMP: cyclic adenosine monophosphate; PGE_1: prostaglandin E_1; PDE-5: phosphodiesterase type-5; ATP: adenosine triphosphate.
Adapted from Porst[6,7]

When seeking help, patients demand treatments that are highly effective (i.e. rigid erection and reliable), easy to use (i.e. rapid onset and reasonable duration of action, with no interference with food and alcohol), with an optimal tolerability and at affordable cost.[10] The importance of having a drug that meets the spontaneous aspect of sexual activity, therefore not requiring advance anticipation, was shown in a study by Fisher et al.;[11] the majority of the couples (two-thirds) engage in sexual activity in a timing and pattern manner that is unpredictable, and only a low proportion (4–5%) usually anticipate their sexual activity.[11] Some factors may limit the use of systemic administration of PDE-5 inhibitors. Except for tadalafil, the rate and extent of absorption of PDE-5 inhibitors (avanafil, sildenafil, and vardenafil) is reduced substantially after a meal. PDE-5 inhibitors show decreases of up to 39% in the peak in plasma concentration (C_{max}) and delays of 1.0–1.25 h in the mean time to the maximum concentration compared with their administration in the fasted state.[12–14]

PDE-5 inhibitors are the first-line on-demand therapy (Level 1a and 1b evidence) for ED.[2] Overall Sexual Encounter Profile (SEP)-3 (SEP question 3 – measure of erectile function [EF] maintenance: 'Did your erection last long enough for you to have successful intercourse?') success rates range between 60% and 75% in mixed ED populations, but decrease below 50% in special difficult-to-treat populations (e.g. cardiovascular disease [CVD], diabetes, radical prostatectomy [RP], hypertension, failure of PDE-5 inhibitor treatment).[2] In patients who have undergone RP, the damage to the autonomic nerve supply to the penis makes PDE-5 inhibitor therapy ineffective.[15] In this group of patients, SEP-3 success rates of 34% and 41%, following treatment with vardenafil or tadalafil (20 mg), respectively, have been reported.[16,17] Similarly, the lowest responses to sildenafil have been reported in patients after RP, although some variation exists between difficult-to-treat patient subgroups.[15]

Compliance with PDE-5 inhibitor treatment has been shown to decrease over time. In a mean follow-up of 1–3 years, overall up to 49% of responders to sildenafil, vardenafil, and tadalafil reported that they had discontinued their treatment.[18,19] Common reasons for discontinuation were effect below expectations, high cost, loss of interest in sex, and inconvenience of obtaining sildenafil.[18,19] Non-effectiveness was the leading reason for discontinuation of sildenafil treatment.[20]

The adverse event (AE) profiles of PDE-5 inhibitors are generally similar. Common systemic AEs include headache (5–15%), flushing (3–14%), dyspepsia (up to 10%), and nasal congestion (2–9%).[21–24]

In summary, there is no ED therapy that can serve all patients effectively and satisfyingly. Even with PDE-5 inhibitors, drop-out rates of >50% are observed – common determinant factors are lack of efficacy, in particular lack of full rigidity and non-tolerable systemic AEs. Because PDE-5 inhibitors are not as effective in patients who have undergone RP or are diabetic, a substantial unmet medical need exists among patients who have ED as a result of these conditions. As highlighted by Prof Porst, all of this evidence indicates that 'there is still room for improvement in the management of ED'.

The First ED Topical Treatment: A New Paradigm?

Professor Ignacio Moncada

Prof Moncada's presentation focussed on the value of topical alprostadil as a new treatment option for patients with ED.

A new topical formulation of alprostadil – mechanism of action

Topical alprostadil cream delivers the efficacy of alprostadil in an 'easy-to-use' formulation that does not involve systemic administration. The vasodilator alprostadil is a synthetic analogue of PGE_1 – equivalent to the naturally occurring PGE_1. Alprostadil cream is formulated in combination with a novel skin permeation enhancer, dodecyl-2-N, N-dimethylamino propionate, which allows rapid and complete absorption of alprostadil through the skin cells (Figure 2).[8,9,25] Alprostadil produces corporal smooth muscle relaxation by the activation of adenylate cyclase and subsequent accumulation of cAMP that in turn results in erection; this mechanism is independent of the nitric oxide–cGMP mechanism.[8,26]

EF is normal after application of alprostadil cream based on haemodynamic parameters (mean peak and end of systolic velocity and mean resistance index measured with Duplex ultrasonography) to those observed with intracavernosal alprostadil injection.[26] Alprostadil cream allows on-demand treatment of ED that only requires a simple and non-invasive method of application.[25]

Clinical significance of alprostadil cream – efficacy and safety profile

The efficacy and safety of alprostadil cream has been demonstrated in Phase II and III clinical trials.[27–29] Results from two multicentre, placebo-controlled, Phase II studies have demonstrated significant improvements in EF based on the change in EF score from baseline to final visit after 6 weeks of treatment with alprostadil cream, in men with mild-to-moderate (n=161) or severe (n=142) ED.[27] Clinically relevant changes from baseline in the International Index of Erectile Function (IIEF-EF) and local EF domain scores were observed for the highest dose (300 µg) in patients with severe ED. Efficacy measures of the ability to achieve erection (change in score relative to baseline for question 3), ability to maintain erection after penetration (change in score relative to baseline for question 4 ['When you attempted sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?']), vaginal penetration success rate (SEP), and patient self-assessment of erection scores were also improved with alprostadil cream.[27] The proportion of patients reporting an improvement in erections, as assessed by the global assessment questionnaire (GAQ: 'While using the study medication, did you feel your erections improved?'), was significantly higher ($p<0.001$) in patients with severe ED treated with alprostadil cream (83% [n=35]) with 300 µg versus placebo (26% [n=35]). Most reported AEs (65% local AE plus 3% systemic AE) were mild or moderate, transient, and localised.[27] In results from a study conducted with pooled data from these two Phase II studies (n=303), alprostadil cream demonstrated increased efficacy versus placebo in a dose-dependent manner (50–300 µg).[26,27]

The efficacy and tolerability of alprostadil cream was confirmed in two Phase III randomised controlled trials conducted in men with moderate-to-severe ED (mean IIEF-EF score: 13.6).[28,29] The first study (n=1,732) included patients with a mean age of 60 years (37% aged >65 years) with a wide range of concomitant comorbidities (diabetes [22%], CVD [32%], prostatectomy [12%], hypertension [48%]) treatments (nitrates or alpha-blockers [16%]), and patients who had previously failed to respond to sildenafil (19%).[28] After 12 weeks of treatment, alprostadil cream 300 µg significantly improved EF and intercourse ability compared with placebo. As observed in

Phase II studies, significant improvements in all efficacy parameters (IIEF-EF, SEP-2, and SEP-3) were observed with alprostadil cream compared with placebo.[28] The majority of the successful attempts took place during the first 30 mins following application of alprostadil cream 300 µg.

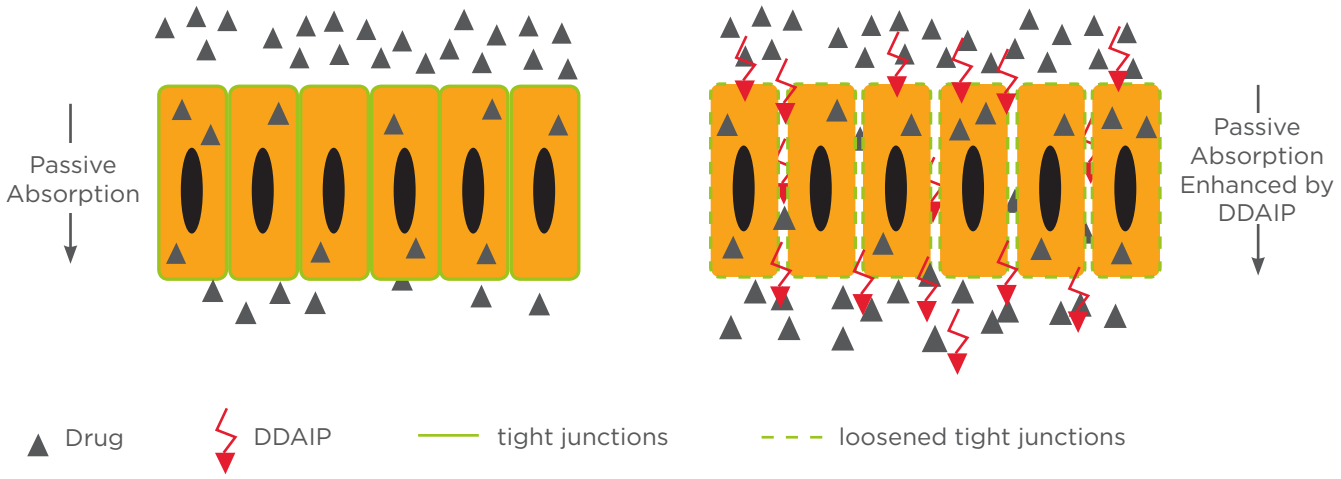

Figure 2: Permeation enhancer dodecyl-2-N,N-dimethylamino propionate (DDAIP) – mechanism of action.
Adapted from Moncada, Cuzin[9]

Table 2: Common adverse effects (AEs) for alprostadil cream 300 µg – results from clinical trials.[9,28]

	Placebo (n=434)	Alprostadil topical cream 300 µg (n=434)
Systemic AEs		
Patient, n (%)		
Overall	3 (0.6)	13 (0.3)
Nervous system	1 (0.2)	11 (1.2)
Dizziness	1 (0.2)	5 (0.5)
Headache	1 (0.2)	N/A
Hyperaesthesia	0 (0)	6
Skin and appendages	1 (0.2)	2 (0.5)
Rash	1 (0.2)	2 (0.5)
Local AEs		
Patient, n (%)		
Overall	51 (0.6)	279 (64.9)
Genital pain	2 (0.5)	76 (17.5)
Penile burning	26 (0.6)	100 (23)
Penile erythema	9 (2.1)	49 (11.3)
Partner, n (%)		
Overall	13 (3)	28 (6.5)
Vaginal burning	8 (1.8)	19 (4.4)
Vaginitis	5 (1.2)	9 (2.1)

As observed in Phase II studies, the majority of AEs were mild-to-moderate, transient, and localised. The long-term (up to 9 months) efficacy and safety profile of alprostadil cream has also been demonstrated in an open-label study conducted with 1,161 patients (mean age 60 years) with mild-to-severe ED (IIEF-EF score ≤25).[29] Most of these patients had participated in the Phase III trials. The majority of the patients (93%) had a mean ED duration of ≥12 months. Patients were initially administered with alprostadil cream 200 µg that could be titrated up or down to 300 µg or 100 µg for up to 9 months (two doses/week). Significant improvements based on the change from baseline in IIEF-EF score were observed after 6 months of treatment (n=119) with alprostadil cream 300 µg (score of 21) compared with placebo (score of 11).[29] As observed in Phase II and III studies, adjustment to 300 µg alprostadil facilitated the greatest improvement in EF, based on SEP-2 and SEP-3 responses.[29]

No major differences compared with placebo have been observed in terms of systemic AEs – as expected from a drug with a local site action.[9,28] The incidence of local AEs, however, was higher among patients treated with alprostadil (65%) compared with placebo (10%) (Table 2).[9,28] All local AEs were mild or moderate and of short duration. In the long term, the incidence of AEs decreased overall (34%).[29]

Results from the clinical studies demonstrate that alprostadil cream can be considered as a valid therapeutic option in patients with ED. Patients who may benefit the most include treatment-naïve patients, patients who do not respond, cannot tolerate, or do not accept PDE-5 inhibitor therapy, and patients treated with nitrates.[25,26,29]

Results of a survey of patients (n=152) asked to express their preferences for an ED treatment according to the route of administration (systemic/oral, injectable, intra-urethral, or cream/topical) showed that 53% of subjects would select a cream as the first choice.[9] In summary, alprostadil is offered in a new formulation, a cream that combines it with a novel skin-permeation-enhancing drug-delivery system. The new topical formulation allows fast onset of action, with reliable efficacy and no anticipated interference with other drugs, food, or alcohol consumption. It is easy to use, well suited for a broad range of patients (e.g. undergoing other therapies) and, more importantly, with low incidence of unexpected systemic AEs.

Alprostadil Cream: Patients Who Could Benefit Most

Doctor Béatrice Cuzin

Dr Cuzin reflected on the population of patients with ED who could benefit the most from treatment with alprostadil cream. As already discussed during the symposium, the efficacy and safety of alprostadil cream has been demonstrated in clinical studies conducted in large study populations.[9,28,29] The studies involved patients across a wide spectrum of disease severity and concomitant conditions and/or treatments. Clinical populations studied included patients who were not candidates for treatment with PDE-5 inhibitors (non-responder, contraindicated), severe ED patients, and difficult-to-treat patients (i.e. failed previous PDE-5 inhibitor therapy [specifically sildenafil], with stable CVD, hypertension, diabetes, those who had undergone prostatectomy, and those aged >65 years). Clinical response was evaluated according to medical history and severity of ED.[9,28,29]

Of special consideration is the interpretation of instruments used to measure patient-reported outcomes recommended by the USA's FDA guidelines and emerging methods.[30] There is a need to provide evidence on outcomes based on qualitative (collecting input directly from patients and clinical experts) and quantitative (use of a particular responder threshold as an indicator of meaningful change from the patient's perspective) methods that can help to draw conclusions about the statistical significance and clinical relevance of the treatment. To evaluate treatment-related changes in terms of clinically relevant improvement it is therefore an essential aspect towards understanding treatment efficacy, interpreting the results across studies, and managing patients effectively.

A new paradigm for patients who are not satisfied with, cannot tolerate, or do not accept PDE-5 inhibitor therapy or other ED treatments

A new treatment for ED can be offered to these patients that could help address their unmet needs with other treatments. Current therapy with ED, usually consisting of systemic treatment with PDE-5 inhibitors, does not always reflect a patient's preference. Patients demand easy-to-use treatments with a rapid onset of action and no interference with food and/or alcohol.[9,10] Acceptable AEs are an important consideration at

the time of selecting treatment for ED. In a study conducted to evaluate the efficacy and safety of alprostadil formulated for intracavernosal treatment, penile pain was very commonly reported (50%), followed by haematoma or ecchymosis (8%) and prolonged erections (5%).[31] The incidence of systemic treatment-related AEs is high with PDE-5 inhibitors. Common AEs include headache (13–16%), flushing and dyspepsia (4–12%), back pain (7%), and myalgia (6%).[2]

Table 3: Two case studies.

Clinical history and examination	Points of discussion	Outcome
Case 1		
• 56-year-old • ED for the past 12 months (difficulty to maintain erections) • Appendectomy (40 years old) • Hypertension for 7 years (bisoprolol) • Ex-smoker • BMI 27 kg/m^2, waist circumference 99 cm, BP 125/80 (under β-blockers), HR 72/min, BPH symptoms, normal genitalia	• Heterosexual, with an intermittent sexual relationship with the same partner (past 18 months) • No history of oral PDE-5 use • IIEF-EF score=15 – moderate ED • Normal FBC and U&E: not diabetic (only possible impaired glucose intolerance), normal levels of cholesterol, testosterone, and PSA • Potential risk of CVD (overweight, hypertension) – systemic treatment could be indicated as first-line • Afraid of the risk of CVD associated with the use of PDE-5 • Unwilling to let the partner take part in the discussion for treatment choices	• Patient opted for topical alprostadil cream 300 µg • Successful outcome with an EF domain score of 27 when using the cream
Case 2		
• Localised prostate cancer diagnosed 12 months earlier • Preoperative PSA 5.4 ng/ml • Robotic RP (bilateral nerve sparing) • Pathology showed T2 Gleason 4+3 adenocarcinoma, negative margins • Married for 35 years (60-year-old wife) • Tadalafil 5 mg/day (from Week 3 after surgery) • No spontaneous or nocturnal erections, even with additional on-demand PDE-5 therapy • IIEF-EF domain score 10	• Had an effective trial dose of intracavernous alprostadil 10 µg, but caused severe pain – unwilling to continue with injections	• Topical alprostadil, cream was used with good efficacy and no major adverse effects

BMI: body mass index; BP: blood pressure; BPH: benign prostatic hyperplasia; CVD: cardiovascular disease; ED: erectile dysfunction; EF: erectile function; FBC: full blood count; HR: heart rate; IIEF-EF: International Index of Erectile Function; MUSE: medicated urethral system for erections; PDE-5: phosphodiesterase type-5; PSA: prostate specific antigen; RP: radical prostatectomy; U&E: urea and electrolytes.

In contrast, common local AEs with alprostadil cream include penile burning sensation (25%) and penile erythema (11%).[25] Furthermore, AEs leading to discontinuation were rarely reported with alprostadil cream – 4.3% reported in clinical trials[29] compared to 12% with PDE-5 inhibitors[19] and >40% with PGE1 intracavernous injections.[2]

Difficult-to-treat patients (diabetes, cardiovascular disease, prostatectomy, hypertension)

Patients with severe ED and comorbidities are of particular concern. Treatment with alprostadil cream significantly improves EF in patients with severe disease in a dose-dependent manner (measured by IIEF-EF, SEP-2, and SEP-3). The proportion of patients in the Phase II study reporting significant improvements in the GAQ score was up to 76% (200 µg) (n=35) and 83% (300 µg) (n=35) compared with 26% in the placebo group (n=35).[27] In a post-hoc analysis of the Phase III studies, clinically significant changes in the IIEF-EF scores were demonstrated across subgroups of patients with different comorbidities (diabetes, CVD, prostatectomy, hypertension) using 300 µg alprostadil regardless of the ED severity.[30]

In summary, topical alprostadil cream has been demonstrated in clinical trials to be effective and well tolerated in the treatment of ED, across a wide spectrum of patients and severities of ED.

In patients with concomitant conditions such as diabetes, hypertension, CVD, or in those who have undergone prostatectomy, treatment with alprostadil cream resulted in significant improvement in EF, reaching the normal range of IIEF-EF, defined as ≥26 score for some patients.[9] The results indicate that alprostadil cream is a valid alternative option for any type of patient with ED. Patients with a history of CVD, sildenafil failure, or prostatectomy treated with alprostadil cream 300 µg show consistent statistically significant improvements in vaginal penetration and EF maintenance.

Following its marketing authorisation by the European Health Authorities in 2013, topical alprostadil has been approved in more than ten countries. Alprostadil cream is the first innovative ED product in nearly a decade, and has the potential to help a large number of patients, including treatment-naïve patients; patients preferring a local treatment for a local problem; patients unable to tolerate or who do not accept PDE-5 inhibitor therapy or other ED treatments; patients over the age of 65 years; difficult-to-treat patients (i.e. diabetes, CVD, prostatectomy, hypertension, PDE-5 failure); patients with CV risk and with CV comorbidities treated with nitrates (except if having strong contraindications for sexual activities); and patients with benign prostatic hypertrophy treated with α-blockers.[9,25]

Clinical Cases: Discussion With the Experts

Doctor Ian Eardley

During the second session of the symposium, the panellists evaluated two clinical cases from their clinical practice. Following a detailed description of each real-world situation by Dr Ian Eardley, panellists had the opportunity to look in depth at each case in order to make decisions about the most appropriate treatment options (Table 3).

Concluding Remarks

Topical alprostadil cream is a valid treatment option for patients affected with ED and can be considered a first-line choice for a wide range of patients. This new formulation of alprostadil combined with a novel skin permeation enhancer allows a local and fast onset of action with reliable efficacy, while maintaining patient acceptability in the long term.

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