New Medicine Assessment

Alprostadil 3 milligram/gram cream (Vitaros®)

Treatment of men ≥ 18 years of age with erectile dysfunction

Recommendation:

Alprostadil 3 mg/g cream is recommended as an alternative to transurethral and intracavernosal alprostadil or vacuum pump devices, for patients with erectile dysfunction in whom at least 2 types of phosphodiesterase 5 (PDE5) inhibitor treatments have failed (with at least 8 tablets consumed, before deciding failure of treatment, for each PDE5i trialled) or in whom there is an intolerance or contraindication to PDE5 inhibitors.

GREEN Restricted
Alprostadil 3 mg/g cream is suitable for initiation and ongoing prescribing in primary care where patients with erectile dysfunction have an intolerance or contraindication to PDE5 inhibitors.

AMBER Level 0
Alprostadil 3 mg/g cream is suitable for prescribing in primary care following recommendation or initiation by a specialist for patients with erectile dysfunction who have experienced treatment failure with at least 2 types of PDE5 inhibitors.

Summary of supporting evidence:

- The efficacy & safety of alprostadil cream is derived from two randomised double-blind studies (n=1732) of 12 weeks duration and one open-label, non-comparative extension study (n=1161) of up to 9 months duration.
- There was a statistically significant mean increase in IIEF-EF score of 2.5 for alprostadil 300 microgram cream compared to a mean decrease for placebo of 0.7 ($p<0.001$). However this does not meet the score of 4 or more which is considered to be the minimum clinically important difference.
- The mean proportion of "successful vaginal penetration intercourse attempts" (SEP2) increased from baseline by 7.6% for those treated with alprostadil 300 microgram cream in comparison to a mean decrease of 4.7% for those treated with placebo ($p<0.001$). Despite this primary outcome being statistically significant, it is not considered a clinically relevant improvement in SEP2.
- The mean proportion of "intercourse attempts leading to ejaculation" (SEP3) for alprostadil 300 microgram cream increased by 9.8% from baseline compared to a 0.9% absolute increase from baseline for those treated with placebo ($P<0.001$). This result is considered to be a clinically relevant improvement.
- A subgroup analysis, requested by the Netherlands Medicines Evaluation Board, reported that close to 40% of men had a clinically significant increase in IIEF-EF score, 36% had a clinically relevant improvement in penetration ability (SEP2) and 31% had a clinically relevant improvement in the ability to have successful intercourse (SEP3).

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- It is noted in the PAR and in the European Urology Guidelines that the efficacy of alprostadil cream for erectile dysfunction is modest at best.

- Only 12% of the intention-to-treat patients were included in the IIEF primary domain analysis at visit 5 (day 180) in the open label trial. The mean change for those treated with 300 microgram dose increased by 10 points.
- After 5 months of treatment with the 300 microgram dose 79% of patients had an IIEF-EF score change >4.

- 2.7% of patients withdrew from the RCTs due to treatment-related adverse events and 4.3% patients discontinued treatment in the non-comparative study due to AEs.
- 12.2% of patients in the 300 microgram alprostadil group in the non-comparative study reported application site reactions. 64.9% patients in the 300 microgram alprostadil group in the RCTs reported urogenital system AEs, of which 23% patients reported penile burning.
- 6.5% of partners in the 300 microgram group of the RCTs reported AEs, including vaginal burning and vaginitis. 3.1% of partners in the non-comparative study reported any AEs.

- The primary endpoints used in these studies are widely accepted appropriate measure of efficacy of ED treatments.
- 18.8% of patients in the main RCTs had previously used and failed on sildenafil therapy, which would be where the preparation could be used.
- The patients included in the trials may not reflect the population that the alprostadil cream would be prescribed in as only 41% were over the age of 65. The patients who agreed to enrol in the non-comparative extension trial may have been more likely to have experienced a response to alprostadil cream in the initial RCTs, which could have led to an over-estimation of the benefits of the alprostadil cream. The non-comparative extension study used intention-to-treat analysis for the safety/adverse events analysis but only patients who were normo-responsive at visit 4, day 60, were permitted to continue treatment. This resulted in 12% of the intention-to-treat population being included in the IIEF primary domain analysis.

- The topical application route for alprostadil cream may be preferred to the alternative transurethral and intracavernosal alprostadil formulations. Alprostadil cream may be prescribed on the NHS only under certain circumstances. There are no safety data for its use beyond 9 months or for its use in oral or anal sex.

- Alprostadil cream costs £10 per dose, which is significantly more than generic sildenafil (currently 29p for 1 x 50 mg tablet). The alternative alprostadil products range from £7.73 - £21.58 for one dose for the intracavernosal injection.

- If 40% of current prescribing of all alprostadil preparations was for alprostadil cream this would be a cost of £39 052 which would be a cost decrease of £7358.

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Details of Review

Name of medicine (generic & brand name)**:** Alprostadil (Vitaros®)
Strength(s) and form(s): 3 mg/g cream (Only this strength available in the UK)
Dose and administration: Each Vitaros® AccuDose container is for single use only. 300 microgram alprostadil applied to the tip of the penis 5–30 minutes before sexual intercourse. Maximum 1 dose in 24 hours and 2–3 doses per week. N.B. The SPC and PIL advise the dose can be lowered to 200 micrograms in those patients who do not tolerate or experience side-effects with the 300 microgram dose. However, on contacting Takeda UK, only the 300 microgram strength of alprostadil cream is commercially available in the UK and there are no plans to market the 200 microgram product. A 200 microgram dose cannot be measured from the 300 microgram single unit dose pack.
BNF therapeutic class / mode of action 7.4.5 Drugs for erectile dysfunction
Licensed indication(s): Treatment of men ≥ 18 years of age with erectile dysfunction (ED), which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
Proposed use (if different from, or in addition to, licensed indication above): For those patients who have either failed PDE5i (phosphodiesterase inhibitor) treatment (Trials of two PDE5i in primary care starting with sildenafil and one other PDE5i with at least 8 tablets consumed before deciding failure of treatment of each) or do not wish to try pump devices.
Course and cost: 300 microgram in 100 milligram cream in single-use prefilled applicator, 4 = £40.00. Maximum 1 dose in 24 hours and 2-3 doses per week
Current standard of care/comparator therapies: Phosphodiesterase type-5 inhibitors (PDE5I)

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Vacuum Pumps and Constrictor Rings
Alprostadil intracavernosal injections
Alprostadil transurethral system
Penile prosthesis

Clinicians should consult local commissioning policies for the currently approved comparator therapies prior to prescribing.

Relevant NICE guidance:

There are no NICE clinical guidelines specifically for the management of ED however a NICE Evidence Summary of a New Medicine was published in December 2014; NICE ESNM50: Erectile dysfunction: Alprostadil cream[1].

There are a range of other conditions which may be associated with ED. ED is discussed in the following NICE guidelines:

NG12 Suspected cancer recognition and referral[2]

- Consider prostate cancer as a possible diagnosis in men suffering with erectile dysfunction. Consider a prostate-specific antigen (PSA) test and digital rectal examination. See primary care investigations for more information on PSA tests and digital rectal examination.

CG87 Type 2 Diabetes Mellitus[3]

- Review the issue of erectile dysfunction with men annually.
- Provide assessment and education for men with erectile dysfunction to address contributory factors and treatment options.
- Offer a phosphodiesterase-5 inhibitor (choosing the drug with the lowest acquisition cost), in the absence of contraindications, if erectile dysfunction is a problem.
- Following discussion, refer to a service offering other medical, surgical, or psychological management of erectile dysfunction if phosphodiesterase-5 inhibitors have been unsuccessful.

Cg108 Chronic Heart Failure[4]
Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including older adults and patients with:

- peripheral vascular disease
- erectile dysfunction
- diabetes mellitus
- interstitial pulmonary disease and
- chronic obstructive pulmonary disease (COPD) without reversibility.

CG175 Prostate cancer: Diagnosis and Treatment[5]

- Ensure that men have early and ongoing access to specialist erectile dysfunction

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services.

- Offer men with prostate cancer who experience loss of erectile function phosphodiesterase type 5 (PDE5) inhibitors to improve their chance of spontaneous erections.
- If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer men vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative.

CG15 Type 1 diabetes[6]
Blood Pressure control - Concerns over potential side effects should not be allowed to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant, in particular:

- direct questioning should be used to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes.

Neuropathy and associated complications –

- Men should be asked annually whether erectile dysfunction is an issue.
- A PDE5i drug, if not contraindicated, should be offered where ED is a problem.
- Referral to a service offering other medical and surgical management of ED should be discussed where PDE5i are not successful.
- The management of the symptoms of autonomic neuropathy should include standard interventions for the manifestations encountered (for example, for ED or abnormal sweating).

CG172 MI – Secondary Prevention[7]
When treating ED, treatment with a PDE5i may be considered in men who have had an MI more than 6 months earlier and who are now stable.

CG35 Parkinson's Disease[8]
Autonomic disturbance - People with PD should be treated appropriately for the following autonomic disturbances:

- urinary dysfunction
- weight loss
- dysphagia
- constipation
- erectile dysfunction
- orthostatic hypotension
- excessive sweating
- sialorrhoea.

CG72 Attention Deficit Hyperactivity Disorder (ADHD)[9]
In young people and adults, sexual dysfunction (that is, erectile and ejaculatory dysfunction) and

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dysmenorrhoea should be monitored as potential side effects of atomoxetine.

Background and context

The European Association of Urology 2015 guidelines on male sexual dysfunction[10] define ED as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. These guidelines advise that addressing lifestyle and other possible causes of ED must precede or accompany any pharmacological treatment.

The guidelines recommend that first-line pharmacological treatment is usually with an oral selective PDE5i. Vacuum erection devices are also recommended as an alternative first-line option. Intracavernosal alprostadil is a second-line pharmacological treatment option for men who cannot tolerate, or have contraindications to, oral treatment with PDE5i or in whom PDE5i are ineffective. The reported drop-out rates for intracavernosal alprostadil are high (41-68%) and it is stated that there is limited compliance. The guidelines go on to state that intraurethral alprostadil is a further alternative second-line option for men who prefer a less invasive but less efficacious

treatment to the intracavernosal route. In addition, topical alprostadil cream is listed as a second-line option for ED in the updated 2015 guidelines. In relation to the cream, the guidelines state that clinical data are limited but significant improvement compared to placebo was recorded for IIEF, SEP2 and SEP3 in a broad range of patients with mild to severe ED.

The British Society for Sexual Medicine also produced guidelines on the management of erectile dysfunction which were updated in 2013.[11] In line with the European guidelines, the British guidelines also recommend addressing lifestyle and other possible causes of ED alongside specific pharmacotherapy. They also recommend the same first and second-line treatment pathways with topical alprostadil cream listed alongside intracavernous and intraurethral alprostadil as a second-line option.

In the UK, alprostadil is licensed for the treatment of ED and is available as the following products: Vitaros® cream, Caverject® intracavernosal injections, Viridal® intracavernosal injections and MUSE® transurethral delivery system.

Treatments for ED, including alprostadil cream but with the exception of generic sildenafil, are only available at NHS expense for men with prostate cancer, kidney failure treated with dialysis or transplantation, spinal cord injury, diabetes, multiple sclerosis, single gene neurological disease, spina bifida, Parkinson's disease, polio or severe pelvic injury, men who have undergone radical pelvic surgery or prostatectomy and for men who were already receiving drug treatment for impotence on the NHS on 14 September 1998. Such prescriptions must be endorsed with "SLS".[12]

Alprostadil cream is only available in the UK in single use containers of 100 mg containing 300 micrograms of alprostadil. Alprostadil is chemically identical to prostaglandin E_1, the actions of which include vasodilatation of blood vessels in the erectile tissues of the corpora cavernosa and increase in cavernosal artery blood flow, causing penile rigidity. After application of alprostadil cream to the tip of the penis, the onset of erection is within 5 to 30 minutes. Alprostadil has a short half-life and improvement of erections may last from 1 to 2 hours after dosing.[13] It should be used no more than once in 24 hours and up to a maximum of two to three times per week. Alprostadil cream also contains an excipient known as dodecyl-2-N, N-dimethylaminopropionate hydrochloride (DDAIP HCl) which optimises absorption of the alprostadil.[14]

The studies identified in this new medicines assessment used the International Index of Erectile Function erectile function (IIEF-EF) domain score as a joint primary outcome (See Appendix B). The IIEF-EF is a validated questionnaire which the patient completes in order to give a measure of erectile function. The lower the score, the worse the dysfunction.[15] Scores are defined as follows: 6-10 severe dysfunction, 11-16 moderate dysfunction, 17-21 mild to moderate dysfunction, 22-25 mild dysfunction, 26-30 no dysfunction. These grades of ED are reported differently in the Araujo paper.[16] A difference of at least 4 points in the erectile function domain is considered a clinically important difference.[17] In addition to the IIEF-EF, other efficacy outcome measures were responses to the Sexual Encounter Profile (SEP), a validated questionnaire which the patient completes themselves.

As the main studies were placebo-controlled or non-comparative, it is not known how alprostadil cream compares to other ED therapies. It may not be valid to extrapolate data of different populations using different interventions. The European guidelines state that efficacy, (measured as erection rigidity sufficient for vaginal penetration, SEP question 2) is seen in 56-84% with PDE5i (depending on drug and dose) compared to 25 - 35% for those taking placebo, up to 90% with vacuum devices, more than 70% of men using intracavernosal alprostadil and 30-65.9% of men using intraurethral alprostadil. Patients who have undergone prostatectomy who are prescribed a PDE5i show variable rates of success depending on type of surgery, type of PDE5i and dose of PDE5i.[10]

Lancashire Medicines Management Group Erectile Dysfunction guidance is currently in development and should be consulted once available.

Summary of evidence

Summary of efficacy data in proposed use:

This evidence review is based on three phase III studies which evaluated the efficacy and safety of alprostadil cream in men with ED. Two of these were randomised controlled trials (RCTs) whereas the third study was an open-label non-comparative extension study which is discussed in more detail in the "other efficacy data" section below.

The two randomised double-blind placebo-controlled parallel-design studies had the same protocol and were published as an integrated analysis.[18] They were carried out over a twelve-week period in a general population of 1732 men, aged 21 years or older (mean age 60 years, 37% older than 65 years) with ED of at least three months' duration. Participants had been in a stable, monogamous, heterosexual relationship for at least 3 months. Notable exclusions from the study were men with ED caused by untreated endocrine disease or significant penile pathology e.g. penile fibrosis or Peyronie's disease. Baseline characteristics were similar across all treatment groups. The study population included men with a wide range of conditions or characteristics as follows: heart disease (29%), diabetes (22.1%), prostatectomy (12.7%) and men in whom PDE5i were ineffective (18.8%).

The RCTs used changes in the IIEF-EF score as a co-primary outcome (See Appendix B for an example). The other primary outcome measures were changes between the baseline (first visit) and final visit at 12 weeks, on the Sexual Encounter Profile (SEP) questions 2 (Were you able to insert your penis into your partner's vagina?) and 3 (Did your erection last long enough for you to complete intercourse with ejaculation?). The minimum clinically important difference in improvement measures are 21% and 23% respectively.[16] Secondary outcomes were the remaining questions of the IIEF-EF and SEP score, Global Assessment Questionnaire (GAQ) and Patient Self-Assessment of Erection. Adverse events, concomitant medication and vital signs were monitored at each study visit.

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The participants were assessed over a 4 week baseline period without any treatment for ED, during which randomisation criteria included at least 4 attempts at sexual intercourse. A 12 week treatment period followed this. At the initial visit, baseline scores on the IIEF-EF domain were assessed and patients were issued with SEP diaries. Men were asked to record attempts at intercourse throughout the study period using SEP diaries. This IIEF questionnaire was completed at 4 weekly visits, in addition to assessing the patient's SEP diary, concomitant medication, adverse events (AEs), vital signs and genital examinations were performed.

All men were randomly assigned to treatment with placebo or 100 microgram, 200 microgram or 300 microgram alprostadil cream. As only the 300 microgram strength of cream is available in the UK, only the results for the 300 microgram strength are reported here. Men were instructed to apply 1 dose of study cream to the tip of the penis approximately 5 to 30 minutes before initiating sexual activity. Up to 24 single doses of the cream were available for the men to use over the 12 week study period.

There was a statistically significant mean increase of 2.5 (from 13.6 to 16.1) for alprostadil 300 mcg cream for the IIEF-EF score compared to a mean decrease of 0.7 (from 14.0 to 13.3) for the placebo treatment arm ($p<0.001$). It is of note that with a score of 16.1 at final visit, the patient would still be classified as having mild to moderate ED (normal score >25). However, despite being statistically significant this score would not be considered as clinically significant as an increase of at least 4 points is considered as being clinically relevant.

The mean percentage change from baseline in proportion of successful intercourse attempts with vaginal penetration (SEP2) was a statistically significant increase of 7.6 percentage points (from 49.9% to 57.5%) for alprostadil 300 microgram cream in comparison to a decrease of 4.7 percentage points (from 55.9% to 51.2%) for placebo ($p<0.001$). This is equivalent to a relative increase in proportion of intercourse attempts of 15.1%. It is noted in the PAR that the improvement in this score for the PDE5i was about 90%. Even taking into account the decrease of 10% seen in the placebo group the improvement is modest. The minimum clinically important difference (MCID) is quoted as 21% [1,16] so although the result is statistically significant, it does not meet what is regarded as clinically significant. (Please note, the MCID may differ dependent on the baseline severity of ED. For patients with moderate severity, as is the case for the patients in the trial, the minimum clinical important difference is quoted in Araujo as 16.7%[16] therefore using this figure, clinical significance was still not met).

The Netherlands Medicines Evaluation Board published a Public Assessment Report (PAR) in November 2013.[14] Due to efficacy concerns raised during the initial registration round, the Netherlands Medicines Evaluation Board requested a post-hoc responder analysis of the total population[16] and this was reported briefly in the PAR. Responder analyses indicated that close to 40% of patients achieved a clinically significant improvement in their IIEF-EF score when treated with either 200 microgram or 300 microgram alprostadil cream. The ability to penetrate the vagina (SEP2) with alprostadil cream was most consistent with the 300 microgram dose with about 36% of the total population given this dose, reporting a clinically relevant improvement. These response rates are less than those reported for other treatments for erectile dysfunction but there are no direct head-to-head comparisons therefore there are limitations to making such

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comparisons in terms of differences in study design and clinical endpoints. The PAR states that similar results to those of all men were generally observed within subpopulations (men who had previously obtained limited benefit from PDE5i and men with diabetes, heart failure, hypertension or who had undergone a prostatectomy).

There was a statistically significant increase for the third primary outcome of mean percentage change from baseline in proportion of intercourse attempts leading to ejaculation (SEP3) for alprostadil 300 microgram cream of 9.8 percentage points (from 28.7% to 38.5%) in comparison to a 0.8 percentage points absolute increase (from 29.4% to 30.3%) for placebo (P<0.001). This is equivalent to a relative increase in the proportion of successful attempts at intercourse leading to ejaculation of 34.1%. The PAR notes the modest improvement produced by the treatment and states that the improvement seen for SEP3 when patients were treated with PDE5i was about 100%. The minimum clinically important difference for SEP3 questions in improvement from baseline to 12 weeks is 23%. Therefore the increase observed is both statistically and clinically significant for this primary outcome.

There was a statistically significant difference in the secondary outcome of percentage of men reporting an improvement in their erections of 52% for alprostadil 300 micrograms cream compared to 20% for placebo. The authors report a significant, dose-dependent improvement in patient satisfaction (P<0.001), as measured by the GAQ, though specific data were not reported for this secondary outcome.

Other efficacy data:

A further open-label, non-comparative extension study was identified in which the majority of the participants were recruited from the RCTs detailed above, but which also included some additional men.[19] The planned duration of the study was originally 12 months but this study ended prematurely after 9 months and the aim was to assess the safety and efficacy of alprostadil cream in long-term use. See safety data section for further information.

1161 patients (998 double-blind rollover; 163 naïve) with ED were enrolled. Male patients were eligible for the study if they were 21 years of age or older and in a stable, monogamous relationship with their consenting partner and had a history of ED for the preceding 3 months or longer. The included men had an IIEF-EF domain score of 25 or less (mild to severe ED). Patients were excluded from the study if they had ED caused by any untreated endocrine disease (i.e. hypopituitarism, hypothyroidism, hypogonadism) or significant penile pathology including but not limited to curvature, fibrosis or Peyronie's disease, sexually transmitted disease, or penile implant. Patients were also excluded if they had a history, within the previous 6 months, of orthostatic hypotension, syncopal episodes, presyncopal symptoms, myocardial infarction, and significant neurological disease such as stroke or spinal cord injury. Patients with evidence of significant hepatic disease or significant renal disease were excluded. No other therapies for the treatment of ED were permitted. All other medications were allowed if the dose was, and expected to remain, stable for the course of the study. Baseline characteristics were similar amongst the 100 micrograms, 200 micrograms and 300 micrograms final dose groups.

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For patients who had completed the previous study they were rolled over, within 14 days, into this open label trial. They also had to have sitting and standing blood pressure and pulse rates taken, weight and height measured, a medical history, current medications and sexual history taken. It is not stated how the patients who were not rolled over from the previous study were treated, in terms of baseline assessments. In clinic tolerability was assessed using the alprostadil 200 microgram cream at visit 2 (day 0). For the first 4 weeks of the study, patients could administer 8 doses of 200 microgram alprostadil cream before intercourse and were instructed to engage in foreplay up to twice a week. Patients were titrated up or down to 300 microgram or 100 microgram depending on if they were hypo or hyper-responsive respectively. At the end of the 30 day test-dose period, 72.9% (846 of 1161) patients chose to up-titrate to the 300 microgram alprostadil dose. Eight doses of the new strength alprostadil cream was supplied for use over the next 30 days. Only those patients who were considered normo-responsive were allowed to continue in the study after this second treatment period. The primary efficacy measure was the IIEF-EF domain score (based on responses to questions 1-5 and question 15). The endpoint was the mean change in IIEF-EF score from baseline to visit 5 (day 180). The IIEF-EF was not administered to patients after they were informed of the study closure. The following secondary outcomes were measured; SEP in diaries and patient self-assessment of erection were assessed at visits 3, 4, 5 and study closure visit. The global assessment questionnaire was assessed at visits 3, 4 and 5. The primary safety measures were patient/partner evaluated adverse events (AEs) (see under safety data below).

141/1161 (12%) of intention-to-treat patients were included in the IIEF primary domain analysis at visit 5 (day 180). Of these 12%, the change from baseline of mean scores was 13, 13.2 and 10 points for 100 microgram, 200 microgram and 300 microgram cream respectively. The PAR states that after 5 months of treatment with the 300 microgram dose of alprostadil cream, 79% of patients had an IIEF-EF score change >4.[qqq] The mean percentage of affirmative responses at study closure (≤ day 270) for the alprostadil 300 microgram group to SEP2 was 80.3% (N=322). Similarly for SEP3, the mean percentage of affirmative responses for the alprostadil 300 microgram group was 61.1% (N=245) at study closure. It is important to note that the responses for SEP2 and SEP3 are calculated based on those patients that completed the diaries and not the intention-to-treat population. It is possible that those who completed the diaries and continuing treatment are more likely to be achieving positive results and so these outcomes have the potential to be biased.

The PAR concluded that alprostadil cream was effective in improving and sustaining erections. This was particularly evident in patients who remained in the study until study closure.

Summary of safety data:

46/1732 (2.7%) of patients withdrew from the RCTs due to treatment-related adverse events.[18] 50/1151 (4.3%) patients discontinued treatment in the non-comparative study because of an AE.[19] Most of the AEs were at the site of application in the urogenital region. 103/846 (12.2%) patients in the 300 microgram alprostadil group in the non-comparative study reported application site reactions[19] whilst 279/434 (64.9%) patients in the 300 microgram alprostadil group in the RCTs reported urogenital system AEs of which 100/434 (23%) patients reported penile burning.[18]

Overall 28/434 (6.5%) of partners in the 300 microgram group of the RCTs reported AEs including

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vaginal burning and vaginitis[18] whilst 26/846 (3.1%) partners in the 300 micrograms of the alprostadil group of the non-comparative study reported any AE.[19]

11/434 (1.2%) of patients in the 300 microgram alprostadil group in the RCTs reported nervous system AEs including dizziness and hyperesthesia.[18]

The SPC lists the following as common side-effects which occur in greater than or equal to 1 in every 100 patients: penile burning; penile pain; penile erythema; genital pain; penile erythema; genital discomfort; genital erythema; erection increased; pruritis genital; penile oedema; balanitis; penile tingling; penile throbbing; penile numbness; urethral pain; rash. In women partners: vulvovaginal burning sensation; vaginitis.[13]

The PAR highlighted that there is a lack of 12 month safety data which is not in line with current European licensing recommendations. It was decided that in this case, 6 month safety data was acceptable because alprostadil is a known active ingredient with an established safety profile. In addition, as the dosing of alprostadil cream is intermittent and it has a short half-life and duration of action, long-term safety issues are unlikely to occur. It is of note that long-term safety information for DDAIP is limited. The Rooney et al study[19] planned to run for 12 months but was stopped prematurely after 9 months by the sponsor and the US Food and Drug Administration (FDA), due to concerns about DDAIP, arising from the results of the Tg.AC mouse carcinogenicity study. This clinical hold was later lifted by the FDA. The PAR states that no events have been reported in alprostadil cream phase III studies that would indicate local carcinogenicity at the application site but also that there is insufficient evidence to conclude that the effect of degeneration of seminiferous tubules in the testis of rabbits as a result of local treatment with DDAIP is not relevant for humans.[14]

In the phase III studies, a small number of serious ischaemic cardiac events were reported in the placebo and 300 microgram groups (2 patients (0.5%) and 6 patients (1.4%) respectively). All the affected men had underlying cardiovascular disease at baseline or risk factors for this. The PAR and SPC state that although there is no clear indication that topical alprostadil cream increases the risk of cardiovascular events (other than the vasodilative effects), it cannot be excluded that people with underlying disease or risk factors are at increased risk in combination with increased sexual and physical activity.[13,14]

Strengths and limitations of the evidence:

Strengths

- Two of the phase III studies[18] were double-blind RCTs in a large general population of men with ED in the USA.
- The primary endpoints used in the studies are commonly used recognised measures of assessing erectile dysfunction treatment.
- 18.8% of patients in the main RCTs had previously used and failed on sildenafil therapy which would be where the preparation could be used.

- Rooney et al[19] used intention-to-treat analysis to assess the safety of the alprostadil cream, however this was not the case for the efficacy analysis.

Limitations

- During their assessment of topical alprostadil, the Netherlands Medicines Evaluation Board questioned the lack of a pre-planned definition of "responders" and "clinically relevant" change from baseline for the three primary co-endpoints of the RCTs.
- It is unclear if there was allocation concealment in the published Phase III studies[18].
- There no confidence intervals reported in the paper.
- Only 41% of men in the RCTs receiving 300 micrograms alprostadil cream were over the age of 65.[18] This may not reflect the patient group you would prescribe this preparation in.
- The study authors of the RCTs noted that baseline mean scores for SEP question 2 were very high – 50% in the alprostadil 300 microgram group. This indicates a relatively high level of erectile function before drug treatment. The authors state that this may have been due to limitations with inclusion criteria, methodology and could be an explanation for the relatively low increases in the primary efficacy results.
- Rooney et al[19] was a non-comparative study therefore one cannot assess whether there would have been an improvement in ED if patients had been given a placebo.
- The patients who agreed to enrol could have been more likely to have experienced a response to alprostadil cream in the initial RCTs which may have led to an over-estimation of the benefits of the alprostadil cream.
- Only patients who were normo-responsive at visit 4, day 60, were permitted to continue treatment.
- Of the intention-to-treat population of 1161 patients, only 141 patients completed the primary endpoint analysis at visit 5, day 180. Therefore only these 141 patients were included in the primary efficacy outcome, rather than the intention-to-treat population.

Summary of evidence on cost effectiveness:

No published evidence on the cost-effectiveness of alprostadil cream in the UK has been identified.

Prescribing and risk management issues:

- Each patient should be instructed by a medical professional on the correct technique for the administration of alprostadil cream prior to self-administration. See SPC and PIL for full details on method of administration. N.B. The tip of the AccuDose™ container should not be inserted into the opening of the penis.
- Please note the SPC and PIL advise the dose can be lowered to 200 micrograms in those

patients who do not tolerate or experience side-effects with the 300 micrograms dose. However, on contacting Takeda UK, only the 300 strength of alprostadil cream is commercially available in the UK and there are no plans to market the 200 product. A 200 microgram dose cannot be measured from the 300 microgram single unit dose packs.

- Alprostadil cream should not be used in patients with any of the following:
  - Underlying disorders such as orthostatic hypotension, myocardial infarction and syncope.
  - Known hypersensitivity to alprostadil or any of the ingredients in Vitaros.
  - Conditions that might predispose them to priapism, such as sickle cell anaemia or trait, thrombocythemia, polycythemia or multiple myeloma or, leukaemia.
  - Abnormal penile anatomy such as severe hypospadias, in patients with anatomical deformation of the penis, such as curvature, and in patients with urethritis and balanitis (inflammation/infection of the glans of the penis).
  - Prone to venous thrombosis or who have a hyperviscosity syndrome and are therefore at increased risk of priapism (rigid erection lasting 4 or more hours).
  - Vitaros should not be used in patients for whom sexual activity is inadvisable as in men with unstable cardiovascular or unstable cerebrovascular conditions.
  - Vitaros should not be used for sexual intercourse with a woman with child-bearing potential, or who are pregnant or lactating, unless the couple uses a condom barrier.
- Topical alprostadil has not been evaluated in men with ED due to a spinal cord injury or other neurological disorders, or in men with severe hepatic or renal impairment.
- Topical alprostadil has not been evaluated for use in oral or anal sex.
- Alprostadil cream should not be used in combination with a PDE5i because an additive increased cardiovascular risk cannot be excluded.
- Clinicians may wish to discuss with patients that the PAR states there is insufficient evidence to conclude that the effect of degeneration of seminiferous tubules in the testis of rabbits as a result of local treatment with DDAIP is not relevant for humans.[14]

Commissioning considerations:

Comparative unit costs:

Drug	Dose per intercourse attempt	Frequency of use	Cost per single dose (excluding VAT)
Alprostadil 3mg/g cream	300 micrograms	Maximum 1 dose in 24 hours and 2-3 doses per week	£10.00
Alprostadil urethral sticks	250-1000 micrograms	Maximum 2 doses in 24 hours and 7 doses per week	£10.95 -£11.56
Alprostadil powder and plus diluent	2.5-40 mcg	Maximum 1 dose in 24 hours and 3 doses per week	£7.73-£21.58
Avanafil tablets	50 mg-200 mg	Maximum 1 dose daily	£2.46-£4.93
Sildenafil tablets	25 mg-100 mg	Maximum 100 mg daily	£0.27-£0.31

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Sildenafil chewable tablets	25 mg-100 mg	Maximum 100 mg daily	£3.31-£4.70
Tadalafil tablets	10-20 mg	Maximum 1 daily	£1.96*-£6.75
Vardenafil tablets and oro-dispersible tablets	5-20 mg	Maximum 1 daily	£1.89-£5.87

*£1.96 per single dose refers to tadalafil once daily dosing every day of the month = £54.99 for 28 tablets.

Costs based on MIMS list prices July15.[20] This table does not imply therapeutic equivalence of drugs or doses.

Vacuum pumps and constrictor rings, to maintain erections, are also available as a treatment option for ED. Prices range from £89.50 to £193.00 for single pumps and £5.00 to £34.00 per constrictor ring. (Drug Tariff July 2015, excluding VAT).[12]

Associated additional costs or available discounts:

There would be no additional costs with this preparation and there are currently no available discounts.

Productivity, service delivery, implementation:

This is an alternative preparation and will therefore have no impact on the services already in place. There would need to be education from the clinician for administration and potential AEs, but this would form part of the review of the patient.

Anticipated patient numbers and net budget impact:

Prescribing data for May 2014-April 2015 for Lancashire shows 2244 items for alprostadil were dispensed), at a total cost of £116,025. Of these items 70 were for alprostadil cream at a cost of £2699.

According to the NICE Evidence Summary for alprostadil cream, the manufacturer of alprostadil cream estimates that by year 5 after launch, approximately 40% men who are currently prescribed intracavernosal and intraurethral alprostadil in the UK, may alternatively receive alprostadil cream (Takeda UK Ltd. Personal communication, August 2014).[1] Specialists involved in the production of the NICE Evidence Summary for alprostadil cream advise this is likely to be an overestimation because of the very modest efficacy and side-effect profile of topical alprostadil cream together with the wider availability of generic sildenafil as a treatment option.

If 40% of current prescribing of all alprostadil preparations was for alprostadil cream this would be a cost of £39 052 which would be a cost decrease of £7358 compared to the alprostadil intracavernosal and intraurethral preparations.

Innovation, need, equity:

The European Urology guidelines for erectile dysfunction recommend that patients not responding to oral drugs may be offered intracavernous alprostadil injections as a second-line therapy due to their high success rate (85%).[10] The guidelines then list intraurethral and topical alprostadil as alternative second-line options. There are a number of invasive and non-invasive preparations available and recommended for use across the localities which are very effective for the management of ED. The cream could offer an alternative less-invasive route which some men may prefer.

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Appendix A: Table: Summary of key alprostadil cream RCTs relevant to use in erectile dysfunction

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Padma-Nathan H and Yeager J An Integrated Analysis of Alprostadil Topical Cream for the Treatment of Erectile Dysfunction in 1732 patients *Urology* 2006;68:386-391	2 randomised, double-blind, placebo-controlled, 12 week treatment period (4 week drug free lead in period), parallel-design studies n=1732	Mean age 60.7yrs Age ≥65yrs n=649 (37.4%) Diabetes n=382 (22.1%) Cardiac n=503 (29%) Prostatectomy n=220 (12.7%) Hypertension n=783 (45.2%) Sildenafil failure n=325 (18.8%) Inclusion criteria • ≥21 years of age • In a stable monogamous relationship with a consenting female partner • H/O ED (defined as inability to	Randomly assigned at visit 3 (start of the 12 week study period) to: (n=434) placebo (n=434) topical alprostadil cream at 100 micrograms (n= 430) topical alprostadil cream at 200mcg (n= 434) received topical alprostadil cream at 300mcg Used at home for 12 weeks. Applied dropwise onto the meatus of the penis for a total of up to 24 single doses. Patients had to engage in foreplay and initiate sexual intercourse within 5 to 30 minutes. Investigators assessed the sexual encounter profile diary, concomitant	Integrated analysis of the 2 RCTs: Change between the first visit (baseline) and final visit scores recorded in the EF domain of the IIEF (see table below Appendix B) and between the baseline and final visit responses noted in the Sexual Encounter Profile (SEP) diaries, relating to questions 2 and 3 which assessed the success of vaginal penetration and maintenance of erection to ejaculation. **IIEF, EF** Placebo: Baseline14.0 End point 13.3	At the end of treatment, the percentage of patients reporting improvement in their erections was assessed from the Global Assessment Questionnaire (GAQ). (The patient was asked, "When using the study medication, did you feel your erections improved?"). Patient satisfaction, as measured by the GAQ, showed a significant (P<0.001) dose-dependent improvement versus placebo. Percentage of patients reporting an improvement in erections during the 12 week course was 40%, 47% and 52% for the 100mcg, 200mcg and 300mcg dose groups versus 20% in the placebo group.	Patient-oriented outcome measure?:Yes Allocation concealment?: Yes Blinded if possible?:Yes Intention to treat analysis?: Questionable as they classed ITT as those who received at least one study dose and one post baseline efficacy evaluation. Therefore there could be patients who used the preparation but did not return for first follow up as no benefit found Adequate power/size?: Does not state Adequate follow-up (>80%)?:Yes

		attain and maintain an erection sufficient to permit satisfactory sexual intercourse) of at least 3 months' duration • Vaginal intercourse Exclusion criteria • ED caused by untreated endocrine disease or significant penile pathology e.g. penile fibrosis or Peyronie's disease	medication, adverse event profile, vital signs, genital examination and IELF questionnaire at 4 weekly intervals throughout the study period	Mean change -0.7 Alprostadil 100mcg cream: Baseline 13.6 End point 15.3 Mean change 1.7 *P* value 0.001 Alprostadil 200mcg cream: Baseline 13.6 End point 16.1 Mean change 2.5 *P* value <0.001 Alprostadil 300mcg cream: Baseline 13.6 Endpoint 16.1 Mean change 2.5 *P* value <0.001 **SEP2** Placebo: Baseline 55.9 End point 51.9 Mean change -4.7 Alprostadil 100mcg cream: Baseline 53.4 End point 56.6 Mean change 3.2 *P* value 0.001	Safety was determined from patient and their partner's reporting of Adverse Events (AEs), from observed AEs and changes in clinical laboratory results, ECGs and vital signs. Patient treatment-related adverse events were reported by a total of 811 men. Headache: Placebo 1 (0.2%) Alprostadil 100mcg cream 5 (1.2%) Alprostadil 200mcg cream 1 (0.2%) Alprostadil 300mcg cream 0 (0%) Nervous system: Placebo 1 (0.2%) Alprostadil 100mcg cream 5 (1.2%) Alprostadil 200mcg cream 7 (1.6%) Alprostadil 300mcg cream 11 (2.5%) Skin rash: Placebo 1 (0.2%) Alprostadil 100mcg cream 2 (0.5%)	Level 1 evidence based on POO, allocation concealment, blinding, intention to treat analysis and follow-up. Risk of bias: low based on the above factors apart from power/size which is unknown.

				Alprostadil 200mcg cream: Baseline 52.9 End point 58.2 Mean change 5.3 *P* value <0.001 Alprostadil 300mcg cream: Baseline 49.9 End point 57.5 Mean change 7.6 *P* value <0.001 **SEP3** Placebo Baseline 29.4 End point 30.3 Mean change 0.8 Alprostadil 100mcg cream: Baseline 31.3 End point 38.9 Mean change 7.6 *P* value 0.001 Alprostadil 200mcg cream: Baseline 27.6 End point 41.9 Mean change 14.3 *P* value <0.001	Alprostadil 200mcg cream 5 (1.2%) Alprostadil 300mcg cream 2 (0.5%) Urogenital system total numbers: Placebo 51 (11.8%) Alprostadil 100mcg cream 186 (42.9%) Alprostadil 200mcg cream 254 (59.1%) Alprostadil 300mcg cream 279 (64.3%) Most commonly reported urogenital system AEs: Genital pain Placebo 2 (0.5%) Alprostadil 100mcg cream 48 (11.1%) Alprostadil 200mcg cream 67 (15.6%) Alprostadil 300mcg cream 76 (17.5%) Penile burning Placebo 26 (6%) Alprostadil 100mcg cream 74 (17.1%) Alprostadil 200mcg cream 106 (24.7%) Alprostadil 300mcg cream 100 (23%)	

				Alprostadil 300mcg cream: Baseline 28.7 End point 38.5 Mean change 9.8 *P* value <0.001	46 patients (2.7%) withdrew from the study because of treatment-related adverse events. Partner treatment-related adverse events were reported by 97 women (5.6%), most commonly, vaginal burning (4.3%), All were transient and resolved within 2 hours. 5 partners (0.4%) withdrew from the study due to treatment-related adverse events. 1 patient with a previous history of cardiovascular disease who was assigned to placebo, died of a sudden cardiac arrest. Laboratory tests were carried out in order to monitor safety by assessing for any changes. However, the outcomes of these tests were not reported in the paper.	

Appendix B - **The International Index of Erectile Function (IIEF-5) Questionnaire**

Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999 Dec;11(6):319-26. © 1999 accessed at http://www.hiv.va.gov/provider/manual-primary-care/urology-tool2.asp 30/6/15

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how	Almost	A few times (much less than half the	Sometimes (about	Most times (much more than half the	Almost

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often were your erections hard enough for penetration?	never/never 1	time) 2	half the time) 3	time) 4	always/always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time)4	Almost always/always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)

	findings	
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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