

# Erectile dysfunction: Alprostadil cream

Evidence summary

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[www.nice.org.uk/guidance/esnm50](http://www.nice.org.uk/guidance/esnm50)

## Key points from the evidence

The content of this evidence summary was up-to-date in December 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

In 2 randomised controlled trials (RCTs) alprostadil 300 microgram cream statistically significantly improved erectile function and intercourse ability compared with placebo but the average absolute benefit was modest and only 31%–40% of men (depending on outcome considered) obtained a clinically relevant response. Most reported adverse events were mild to moderate, transient and localised. There are no long term safety data for the use of alprostadil cream and its excipients in treating erectile dysfunction and there are no published comparisons with other drug treatments.

**Regulatory status:** Alprostadil cream ([Vitaros](#)) received a European marketing

authorisation in August 2013 and was launched in the UK in June 2014.

| Effectiveness  | Safety   |
|--|--|
| <ul style="list-style-type: none"> <li>• In 2 RCTs (n=1732) and compared with baseline, alprostadil 300 microgram (410 men) produced a mean:                             <ul style="list-style-type: none"> <li>– 2.5 point increase in the 30-point International Index of Erectile Function erectile function (IIEF-EF) domain score.</li> <li>– 15.1% relative increase in proportion of intercourse attempts with successful penetration (7.6 percentage points absolute increase).</li> <li>– 34.1% relative increase in proportion of attempts at intercourse successful to ejaculation (9.8 percentage points absolute increase).</li> </ul> </li> </ul> <p>All outcomes were statistically significantly different from placebo but only the last one met the criteria for clinical relevance.</p> <ul style="list-style-type: none"> <li>• A post-hoc analysis 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 and 31% had a clinically relevant improvement on ability to have successful intercourse.</li> </ul> | <ul style="list-style-type: none"> <li>• Adverse events were reported in 67% of men using alprostadil cream and 12% of men using placebo, and in 7% and 3% of partners respectively (no statistical analyses reported).</li> <li>• The <u>summary of product characteristics</u> states that commonly reported adverse events are transient, localised urogenital effects including penile burning, pain and erythema in men, and vaginal burning and vaginitis in female partners.</li> <li>• Treatment discontinuation due to adverse events occurred in around 3–4% of participants in clinical trials</li> <li>• Alprostadil cream should not be used in combination with oral selective phosphodiesterase type-5 (PDE5) inhibitors because an additive increased cardiovascular risk cannot be excluded.</li> <li>• The <u>summary of product characteristics</u> advises that the dose may need to be reduced in response to side-effects or in men with hepatic or renal insufficiency, but only a 300 microgram single-dose product is available.</li> <li>• There are no safety data for use beyond 9 months or for use in anal or oral sex.</li> </ul> |

|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• These response rates are less than those reported with other treatments for erectile dysfunction but there are no direct head-to-head comparisons and indirect comparisons are limited by differences in study design and clinical endpoints.</li> </ul>   |   |
| <p><b>User factors</b></p> <ul style="list-style-type: none"> <li>• <a href="#">European guidelines on erectile dysfunction</a> advise that alprostadil offers an alternative choice for men who cannot tolerate or have contraindications to PDE5 inhibitors or in whom they are ineffective.</li> <li>• Alprostadil cream has similar contraindications, cautions and interactions to other alprostadil formulations.</li> <li>• The topical application route may be preferred to the intraurethral or intracavernosal route by some men.</li> <li>• The licensed maximum frequency of use is no more than 2–3 times per week and only once per 24-hour period.</li> </ul> | <p><b>Resource implications</b></p> <ul style="list-style-type: none"> <li>• Alprostadil cream costs £10 per dose, which is significantly more than generic sildenafil but is slightly less costly than other alprostadil products, at usual therapeutic dose.</li> <li>• Department of Health amended <a href="#">regulations</a> allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction. Avanafil, branded sildenafil, tadalafil, vardenafil, and alprostadil may be prescribed on the NHS only under certain circumstances.</li> </ul> |

## Introduction and current guidance

NICE has not published a clinical guideline on erectile dysfunction, although erectile dysfunction is referred to in several NICE guidelines (see [Relevance to NICE guidance programmes](#) for more information). The [European Association of Urology 2014 guidelines on male sexual dysfunction](#) define erectile dysfunction as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction (ED) affects physical and psychosocial health and has a significant impact on

the quality of life for men and their partners. The [European guidelines](#) advise that addressing lifestyle and other possible causes of ED must precede or accompany any pharmacological treatment. According to the [guidelines](#), first-line pharmacotherapy is usually an oral selective phosphodiesterase type-5 (PDE5) inhibitor (avanafil, sildenafil, tadalafil or vardenafil). Non-pharmacological treatment options are also available.

[Full text of Introduction and current guidance.](#)

## Product overview

This evidence summary considers the efficacy and safety of alprostadil cream, a new topical formulation of a drug already licensed for treating erectile dysfunction. Alprostadil is chemically identical to prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and causes vasodilation of blood vessels. Alprostadil cream ([Vitaros](#)) received a European marketing authorisation for the treatment of erectile dysfunction in adult men in August 2013. It was approved through the European Decentralized Procedure; Netherlands acted as the Reference Member State and it was launched in the UK in June 2014.

The [summary of product characteristics](#) states that after application of alprostadil cream to the tip of the penis, the onset of erection is within 5 to 30 minutes. Improvement of erections may last from 1 to 2 hours after dosing. Alprostadil cream has similar contraindications, cautions and interactions to other alprostadil formulations.

[Full text of Product overview.](#)

## Evidence review

- This evidence summary is based on 3 phase III studies that evaluated the efficacy and safety of alprostadil cream in men with erectile dysfunction. Two of the studies were [randomised controlled trials](#) (RCTs) in a general population, with a 12 week treatment period, using the same protocol, and were published as an integrated analysis ([Padma-Nathan et al. 2006](#)).

- Alprostadil 300 microgram produced a mean 2.5 point increase in the 30-point International Index of Erectile Function erectile function (IIEF-EF) domain score, a mean 15.1% relative increase in proportion of intercourse attempts with successful penetration and a mean 34.1% relative increase in proportion of attempts at intercourse successful to ejaculation. All outcomes were statistically significantly different from placebo but only the last met the criteria for clinical relevance.
- A post-hoc analysis 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 and 31% had a clinically relevant improvement in ability to have successful intercourse.
- A statistically significantly greater proportion of men in the alprostadil 300 microgram group than in the placebo group reported improved erections (52% compared with 20%,  $p < 0.001$ ).
- An open-label long-term extension study ([Rooney et al. 2009](#)) reported on alprostadil cream use over a 9 month period. As this study did not compare alprostadil cream directly with an active treatment or placebo (non-comparative), it is not discussed in detail in this evidence summary.
- The [summary of product characteristics](#) states that the most common adverse events reported in clinical studies were transient, localised urogenital adverse effects. The majority of adverse events were mild to moderate in severity, resulting in small numbers of discontinuations (2.7% in [Padma-Nathan et al. 2006](#) and 4.3% in [Rooney et al. 2009](#)).
- Most commonly reported partner adverse events were transient local vaginal reactions (3% in the placebo group versus 6.5% in the alprostadil group). Study withdrawals due to partners' treatment-related adverse events were infrequent (0.4% in [Padma-Nathan et al. 2006](#)).
- There are no safety data for alprostadil cream use longer than 9 months duration or for use in anal or oral sex.
- The 2 RCTs were placebo-controlled and it is not known how alprostadil cream compares to other alprostadil products or PDE5 inhibitors.

[Full text of Evidence review.](#)

## Context

Alprostadil (prostaglandin E<sub>1</sub>) is currently licensed and available in products for intracavernosal ([Caverject](#), [Viridal](#)) or intraurethral ([MUSE](#)) treatment of erectile dysfunction. Alprostadil is recommended as an alternative therapeutic option for men who cannot tolerate or have contraindications to oral treatment with PDE5 inhibitors or in whom PDE5 inhibitors are ineffective. Non-pharmacological treatment options for erectile dysfunction, such as vacuum erection devices, are also available.

[Full text of Context.](#)

## Estimated impact for the NHS

Alprostadil cream is an alternative route of administration that may be preferred to intracavernosal ([Caverject](#), [Viridal](#)) or intraurethral ([MUSE](#)) administration by some men with ED. Although direct comparison studies have not been reported, indirect comparisons suggest that alprostadil is generally less effective than PDE5 inhibitors and is recommended in [European guidelines](#) as a second-line treatment option. The [summary of product characteristics](#) advises that the dose may need to be reduced in response to side effects or in men with hepatic or renal insufficiency, but only a 300 microgram single dose product is available.

As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of alprostadil cream for erectile dysfunction. Alprostadil cream is slightly less costly than alprostadil for intracavernosal injection or intraurethral application, at usual therapeutic dose, but costs substantially more than generic sildenafil (£10 per dose compared with £0.28 to £0.31 per dose for 25 mg to 100 mg tablets respectively).

The Department of Health has amended [regulations](#) to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction. Avanafil, tadalafil, vardenafil, branded sildenafil and alprostadil may be prescribed on the NHS only under certain circumstances (see individual preparations in the [British National Formulary](#)).

[Full text of Estimated impact for the NHS.](#)

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## Full evidence summary

### Introduction and current guidance

NICE has not published a clinical guideline on erectile dysfunction (ED). The [European Association of Urology 2014 guidelines on male sexual dysfunction](#) define ED as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. ED affects physical and psychosocial health and has a significant impact on the quality of life of men and their partners. The [NICE clinical knowledge summary on ED](#) notes that it is associated with physical causes such as diabetes mellitus, hypertension and radical prostatectomy; psychological or emotional causes such as relationship problems or mental health problems; and the use of certain drugs such as antihypertensive drugs.

The [European guidelines](#) advise that addressing lifestyle and other possible causes of ED must precede or accompany any pharmacological treatment. First-line pharmacotherapy is usually an oral selective phosphodiesterase type 5 (PDE5) inhibitor (avanafil, sildenafil, tadalafil or vardenafil), assuming there are no contraindications or drug interactions. Other treatment options include vacuum erection devices and intracavernosal or intraurethral alprostadil (prostaglandin E<sub>1</sub>). Surgical implantation of a penile prosthesis may be considered in men for whom pharmacotherapy is unsuitable. See [Context](#) for more information on alternative treatments.

Several published NICE guidelines make recommendations about identifying and managing ED in specific patient groups (see [Relevance to NICE guidance programmes](#) for more information).

## Product overview

### Drug action

Alprostadil is chemically identical to prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and causes vasodilation of blood vessels in the erectile tissue of the corpora cavernosa and an increase in intracavernosal artery blood flow, resulting in an erection. The excipient dodecyl-2-N, N-dimethylaminopropionate hydrochloride (DDAIP) is added to the formulation of the cream to optimise the absorption of alprostadil (see the [summary of product characteristics](#)).

### Licensed therapeutic indication

Alprostadil cream ([Vitaros](#)) received a European marketing authorisation for the treatment of ED in men aged 18 years and older in August 2013. It was approved through the European Decentralized Procedure; Netherlands acted as the Reference Member State. It was launched in the UK in June 2014.

The [summary of product characteristics](#) states that the onset of erection is within 5 to 30 minutes. Improvement of erections will last approximately 1 to 2 hours, but will vary from person to person. Alprostadil cream has similar contraindications, cautions and interactions to other alprostadil formulations. For example, it is not recommended in men with unstable cardiovascular disease, previous myocardial infarction, orthostatic hypotension or predisposition to priapism. It is also contraindicated in men with abnormal penile anatomy. Concomitant administration with other erectile dysfunction agents is not recommended and no interaction studies have been performed for its use with sympathomimetics, antihypertensives, vasodilators, anticoagulants and antiplatelets. See the [summary of product characteristics](#) for alprostadil cream for full details.

Alprostadil cream has not been studied in men with renal or hepatic impairment and the [summary of product characteristics](#) states that the dose may need to be lowered in these men or in response to side effects, although only one formulation strength is available in the UK.

### Course and cost

Alprostadil 300 micrograms in 100 mg of cream is available in single dose containers. The

cream is applied to the tip of the penis (meatus) 5–30 minutes before attempting intercourse. The maximum frequency of use is 2–3 times per week and only once per 24 hour period. Alprostadil cream costs £40 per pack of 4 doses ([MIMS](#) October 2014, cost excluding VAT).

## Evidence review

This evidence summary is based on 3 phase III studies that have evaluated the efficacy and safety of alprostadil cream in men with ED. Two of the studies were [randomised controlled trials](#) (RCTs) in a general population, with a 12 week treatment period. Both had the same protocol and were published as an integrated analysis ([Padma-Nathan et al. 2006](#)); they provide the main body of efficacy data. The third study was an open-label, non-comparative extension study ([Rooney et al. 2009](#)), in which most of the participants were recruited from the comparative phase III studies but also included some additional men. The intended duration of this study was 12 months but it was closed after 9 months by the study sponsor. This study is not discussed in detail in this evidence summary because of its non-comparative nature. Information from the studies has been supplemented and clarified using the [Netherlands public assessment report \(PAR\) for alprostadil cream](#).

The studies used changes in the [International Index of Erectile Function](#) erectile function domain (IIEF-EF) score as a joint primary outcome. The IIEF-EF is a self-administered questionnaire that gives a measure of erectile function. Lower scores indicate worse dysfunction ([Cappelleri et al. 1999](#)):

- 6–10, severe dysfunction
- 11–16, moderate dysfunction
- 17–21, mild to moderate dysfunction
- 22–25, mild dysfunction
- 26–30, no dysfunction.

The minimal clinically important difference on the erectile function domain is 4 points ([Rosen et al. 2011](#)).

Other outcome measures were specific responses to [Sexual Encounter Profile](#) (SEP), which

is a validated 6 item self-administered questionnaire. SEP question 2 asks 'Were you able to insert your penis into your partner's vagina?' and SEP question 3 asks 'Did your erection last long enough for you to complete intercourse with ejaculation?' The minimal clinically important differences improvement measure, calculated using change from baseline to 12 weeks, on the SEP 2 and SEP 3 questions are 21% and 23% respectively ([Araujo et al. 2012](#)).

**RCTs evaluating the safety and efficacy of alprostadil in men with erectile dysfunction in the general population ([Padma-Nathan et al. 2006](#))**

- Design: 2 [randomised](#), [double-blind](#), [placebo](#)-controlled, 12 week treatment period, parallel-design studies undertaken in 82 centres in the US ([Padma-Nathan et al. 2006](#)) n=1732
- Population: the studies enrolled men aged 21 years or older (mean age 60 years, 37% older than 65 years) with ED (defined as in the [European guidelines](#)) of at least 3 months duration (mean IIEF-EF scores at baseline were 14.0 and 13.6 for placebo and 300 microgram group respectively). Participants had been in a stable, monogamous, heterosexual relationship for at least 3 months. Men were excluded from the study if they had erectile dysfunction caused by any untreated endocrine disease or significant penile pathology but otherwise included a wide general population including men with heart disease (29%), with diabetes (21%), having undergone prostatectomy (12%), taking nitrates or alpha-blockers (16%) and men in whom PDE5 inhibitors were ineffective (18%) The baseline demographic characteristics were similar across all treatment groups.
- Follow-up: Men were assessed during a 4 week baseline period without treatment for ED. This was followed by a 12 week treatment period. Randomisation criteria included at least 4 attempts at sexual intercourse during the non-treatment period. At the initial visit men provided baseline scores on the IIEF-EF domain score. This questionnaire was completed at each 4-weekly study visit. Throughout the study, men were asked to record attempts at intercourse in SEP diaries.

- Intervention and comparison: all men were randomly assigned to treatment with placebo or 100 microgram, 200 microgram or 300 microgram topical alprostadil cream. The 100 microgram and 200 microgram strengths of alprostadil cream products are not available in the UK and so the results for these strengths are not discussed in this evidence summary. Men were instructed to apply 1 dose of study cream to the meatus of the penis approximately 5 to 30 minutes before initiating sexual activity. Men were able to use up to 24 single doses during the 12 week treatment period.
- Outcomes: 3 co-primary efficacy outcomes were used in the studies:
  - change in score of the erectile function domain of the IIEF-EF from baseline to the final visit responses.
  - change between the baseline and final visit responses noted in the SEP diaries relating to question 2 (SEP2).
  - change between the baseline and final visit responses noted in the SEP diaries relating to question 3 (SEP3).

Secondary endpoints were 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.

**Table 1 Summary of RCT studies in men with erectile dysfunction**  
(Padma-Nathan et al. 2006)

|  | Placebo                             | Alprostadil<br>300 microgram <sup>a</sup> | Analysis                                   |
|--|-------------------------------------|---|--|
| Randomised   | n=434                               | n=434                                     |  |
| <b>Efficacy<sup>b</sup></b><br>ITT                                       | n=411                               | n=410                                     |  |
| Primary outcome 1: Mean change in the IIEF-EF domain score from baseline | 0.7 decrease<br>(from 14.0 to 13.3) | 2.5 increase<br>(from 13.6 to 16.1)       | LS mean difference from placebo<br>p<0.001 |

|   |                                     |                                     |  |
|---|-------------------------------------|-------------------------------------|--|
| Primary outcome 2: Mean % change from baseline in proportion of intercourse attempts with vaginal penetration (SEP2) <sup>c</sup> | 4.7% decrease (from 55.9% to 51.2%) | 7.6% increase (from 49.9% to 57.5%) | LS mean difference from placebo<br>p<0.001 |
| Primary outcome 3: Mean % change from baseline in proportion of intercourse attempts leading to ejaculation (SEP3) <sup>d</sup>   | 0.9% increase (from 29.4% to 30.3%) | 9.8% increase (from 28.7% to 38.5%) | LS mean difference from placebo<br>p<0.001 |
| <b>Selected secondary outcomes</b>  |                                     |                                     |  |
| % of men reporting an improvement in their erections  | 20%                                 | 52%                                 | p<0.001                                    |
| <b>Safety<sup>e</sup></b>   | n=434                               | n=434                               |  |
| Men reporting adverse events  | 12.4% (54/434)                      | 67.3% (292/434)                     | No analysis reported                       |
| Urogenital system adverse events <sup>f</sup>   | 10.6% (51/434)                      | 64.9.0% (279/434)                   | No analysis reported                       |
| Partners reporting adverse events <sup>g</sup>  | 3.0% (13/434)                       | 6.5% (28/434)                       | No analysis reported                       |

Abbreviations: IIEF, International Index of Erectile Function; ITT, intention-to-treat; LS, least squares; p, p value.

<sup>a</sup> Only available product strength in UK. The results for the 100 microgram and 200 microgram group are therefore not reviewed in this evidence summary.

<sup>b</sup> Efficacy analyses were based on the ITT population, which included all randomised men who took at least 1 dose of study medication and had at least 1 post-treatment efficacy measurement.

<sup>c</sup> SEP2 = "Were you able to insert your penis into your partner's vagina?"

<sup>d</sup> SEP3 = "Did your erection last long enough for you to complete intercourse with ejaculation?"

<sup>e</sup> Safety analyses included all randomised men who took at least 1 dose of study medication and had at least 1 post-treatment safety measurement.

<sup>f</sup> Urogenital adverse events included penile burning, genital pain and penile erythema

<sup>g</sup> Partner-reported adverse events were vaginal burning and vaginitis

## Clinical effectiveness

The comparative phase III studies ([Padma-Nathan et al. 2006](#)) included 100 microgram and 200 microgram strengths of alprostadil cream, but these are not available in the UK, so only the results for the 300 microgram and placebo treatment groups are discussed in this evidence summary (except where only total combined results are reported, for example participant withdrawals). The mean improvements in the 3 primary efficacy measures with 300 microgram alprostadil cream were statistically significant compared with placebo (table 1). However, the degree of improvement from baseline in IIEF-EF score and in penetration success (SEP question 2) were less than that accepted as being clinically relevant. Only the improvement in percentage of sexual intercourse attempts leading to ejaculation (SEP question 3) was clinically relevant.

Selected secondary endpoints showed a statistically significant improvement compared to placebo. For example the percentage of men reporting improved erections (table 1) and patient satisfaction scores, as measured by the GAQ (data not reported,  $p < 0.001$ ).

During their assessment of topical alprostadil, the Netherlands [Medicines Evaluation Board](#) requested a post-hoc responder analysis, which was reported briefly in the [PAR](#). This states that close to 40% of men treated with the 300 microgram dose obtained a clinically relevant improvement in IIEF-EF score, 36% had a clinically relevant improvement in

vaginal penetration ability and 31% had a clinically relevant improvement in ability to have successful intercourse to ejaculation. The [public assessment report](#) states that similar results to those of all men were generally observed within subpopulations (men who had previously obtained limited benefit from PDE5 inhibitors and men with diabetes, heart disease, hypertension or who had undergone a prostatectomy).

## Safety and tolerability

The [PAR](#) states that in the 2 comparative phase III trials ([Padma-Nathan et al. 2006](#)), 1732 men were treated, of whom 434 received placebo and 1298 received active treatment with alprostadil in doses of 100 microgram, 200 microgram and 300 microgram. Men received treatment for a 12 week duration with a mean of 17–18 applications per person. The phase III open-label extension study ([Rooney et al. 2009](#)) yielded data on 300 men exposed for more than 6 months, and 148 men exposed for up to 9 months. In addition, 120 men had exposure for up to 10 months to the excipient DDAIP in both the drug and placebo. Twelve month safety data are absent because the study was stopped prematurely by the study sponsor and the US Food and Drug Administration (FDA), due to concerns about DDAIP arising from 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.

In the phase III studies a small number of serious ischaemic cardiac events were reported in the placebo and 300 microgram group (0.5% and 1.4% respectively). All the affected men had underlying cardiovascular disease at baseline or risk factors and the [PAR](#) states that none of the events were considered product-related. The [PAR](#) concludes that although there is no clear indication that topical alprostadil cream increases the risk of cardiovascular events, it cannot be excluded that people with underlying disease or risk factors are at increased risk in combination with increased sexual or physical activity.

Most reported side effects were localised to the application site, showed a dose effect and were mild to moderate in severity. In the comparative phase III studies ([Padma-Nathan et al. 2006](#)) the most frequently reported treatment-related adverse events included penile burning, genital pain and penile erythema (23.0%, 17.5%, 11.3% respectively, table 1). Most of these adverse events resolved within 2 hours. In the longer term study ([Rooney et al. 2009](#)) application site reactions (penile burning or erythema) occurred in 12.2% of men using the 300 microgram dose, application site pain was reported by 4.4% of men and 1.3% men reported penis disorders (prolonged or painful erections).

In the comparative phase III studies ([Padma-Nathan et al. 2006](#)), partner treatment-related adverse events were reported in 6.5% (28/434) of women but all were transient and resolved within 2 hours. The most common partner treatment-related adverse event was vaginal burning (4.3%, table 1). Five men (0.4%) withdrew from the phase III studies due to their partners' treatment-related adverse events.

Systemic vasodilation symptoms were reported infrequently. Small numbers of men in the 300 microgram alprostadil cream treatment group experienced dizziness, hypotension or syncope (0.4% in [Padma-Nathan et al. 2006](#)).

## Evidence strengths and limitations

The phase III studies ([Padma-Nathan et al. 2006](#)) were double-blind randomised RCTs in a large general population of men with erectile dysfunction in the US. However, specialists involved in the production of this evidence summary have advised that this study may not reflect the patient cohort seen within the UK. Only 41% of men receiving alprostadil 300 micrograms were over the age of 65. The specialists advise that erectile dysfunction severity increases with increasing age, and it is not clear if the response to alprostadil cream is dependent upon the man's initial IIEF-EF score.

The results reported in the comparative phase III studies ([Padma-Nathan et al. 2006](#)) for the 410 men that used the 300 microgram dose of alprostadil cream available in the UK, demonstrate a modest, but statistically significant effect over placebo. The primary endpoints used in the studies are commonly used in erectile dysfunction literature. However the study design had some 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 3 co-primary endpoints.

The published report of the phase III studies ([Padma-Nathan et al. 2006](#)) provides limited detail on inclusion and exclusion criteria and it is unclear if [treatment allocation was concealed](#). No [confidence intervals](#) are reported for the data in the RCTs. [The study](#) authors note that the baseline mean scores for SEP question 2 were very high in this study (50% in the alprostadil 300 microgram group) indicating a relatively high level of erectile function before drug treatment. The authors go on to state that this may have been due to limitations with inclusion criteria methodology and could have contributed to the relatively low increases in the primary efficacy results.

The limitations of the open-label extension study (Rooney et al. 2009) include the lack of a comparator, and the possibility that men who experienced a response to topical alprostadil in the qualifying studies may have been more likely to enrol than men who did not, potentially over-estimating the benefits of alprostadil. Dropout rates were around 3% in the combined RCTs and 5% in the long-term extension study. However, analyses were by intention-to-treat and few discontinuations were due to adverse events.

The Medicines Evaluation Board acknowledged in the PAR that lack of 12 month safety data is not in line with current European licensing recommendations. The Board decided that data for 6 months were acceptable because alprostadil is a known active substance with an established safety profile. The report concluded that in addition, given the intermittent dosing of alprostadil cream and its short half-life and duration of action, long-term safety issues are not likely to occur. Data on the long-term safety information of DDAIP are limited. For example, the PAR states that there is insufficient evidence to conclude that the effect of degeneration of seminiferous tubules in the testis of rabbits due to local treatment with DDAIP is not relevant for humans.

The numerous exclusion criteria of the studies are reflected in the contraindications and special warnings and precautions for use in the summary of product characteristics. For example, topical alprostadil has not been evaluated in men with erectile dysfunction due to spinal cord injury or other neurological disorders, or in men with severe renal or hepatic impairment or for use in oral or anal sex.

The main studies were placebo-controlled or non-comparative. It is not known how topical alprostadil cream compares to other erectile dysfunction therapies. Extrapolation of data from different populations using different interventions may not be valid. According the European guidelines, efficacy (erection rigidity sufficient for vaginal penetration, SEP question 2) is seen in 56%–84% with PDE5 inhibitors (depending on drug and dose), up to 90% of men using vacuum erection devices, more than 70% of men using intracavernosal alprostadil and 30–66% of men using intraurethral alprostadil.

## Context

### Alternative treatments

The European Association of Urology guidelines on male sexual dysfunction (2014) advise that first-line treatment of erectile dysfunction is usually with an oral selective

PDE5 inhibitor, assuming there are no contraindications or drug interactions. The choice of PDE5 inhibitor depends on the frequency of intercourse and the man's personal experience of these drugs, as well as efficacy, safety and cost.

Vacuum erection devices are also recommended as an alternative first-line treatment option for ED in the [European guidelines](#), with high response rates reported but a wide range of user satisfaction rates (27% to 94%).

Alprostadil (prostaglandin E<sub>1</sub>) is currently licensed and available in products for intracavernosal ([Caverject](#), [Viridal](#)) or intraurethral ([MUSE](#)) treatment of erectile dysfunction. Alprostadil is recommended in the [European guidelines](#) as an alternative pharmacological therapeutic option for men who cannot tolerate or have contraindications to oral treatment with PDE5 inhibitors or in whom PDE5 inhibitors are ineffective. The [guidelines](#) state that intracavernosal alprostadil is associated with high drop-out rates (41–68% reported) and limited compliance. The [guidelines](#) advise that intraurethral alprostadil provides an alternative choice for men who may prefer a less-invasive but less-efficacious treatment to intracavernous injection.

## Costs of erectile dysfunction treatments

|   | Dose per intercourse attempt <sup>a</sup> | Frequency of use <sup>a</sup>                     | Cost per single dose <sup>a</sup> (excluding VAT) |
|---|---|---|---|
| Alprostadil 3 mg/g cream  | 300 micrograms                            | Maximum 1 dose in 24 hours and 2–3 doses per week | £10 <sup>b</sup>                                  |
| Alprostadil urethral sticks                                     | 250–1000 micrograms                       | Maximum 2 doses in 24 hours and 7 doses per week  | £11.30–£11.56 <sup>c</sup>                        |
| Alprostadil powder and solvent for solution for injection vials | 2.5–40 micrograms                         | Maximum 1 dose in 24 hours and 3 doses per week   | £7.73–£21.58 <sup>c</sup>                         |
| Avanafil tablets  | 50 mg–200 mg                              | Maximum 1 daily                                   | £2.46–£4.93 <sup>b</sup>                          |
| Sildenafil tablets <sup>d</sup>                                 | 25 mg–100 mg                              | Maximum 1 daily                                   | £0.28–£0.31 <sup>c</sup>                          |
| Tadalafil tablets <sup>e</sup>                                  | 10–20 mg                                  | Maximum 1 daily                                   | £6.75 <sup>c</sup>                                |

|   |         |                 |                          |
|---|---------|-----------------|--------------------------|
| Vardenafil <sup>d</sup> tablets   | 5–20 mg | Maximum 1 daily | £1.89–£5.87 <sup>c</sup> |
| <p><sup>a</sup> Doses taken from the <a href="#">summaries of product characteristics</a>. The doses shown do not imply therapeutic equivalence.</p> <p><sup>b</sup> Costs taken from <a href="#">MIMS</a>, October 2014.</p> <p><sup>c</sup> Costs taken from <a href="#">Drug Tariff</a>, October 2014.</p> <p><sup>d</sup> Chewable/oral dispersible tablets also available.</p> <p><sup>e</sup> Tadalafil is also licensed for a once daily regimen for men who anticipate a frequent use of tadalafil (for example, at least twice weekly), based on patient choice and the physician's judgement. The recommended daily dose is 5 mg; cost £54.99 per 28 days (<a href="#">Drug Tariff</a>, October 2014, excluding VAT).</p> |         |                 |                          |

Vacuum pumps (manually or battery operated devices) and constrictor rings (to maintain erection) are also available as a treatment option for ED. Prices range from £89.50 to £191.58 for single pumps and £4.00 to £17.53 per constrictor ring. ([Drug Tariff](#), October 2014, excluding VAT).

## Estimated impact for the NHS

### Likely place in therapy

[European guidelines](#) advise that any pharmacological treatment should be part of a package of care for the management of ED. This should include identifying and addressing any underlying cause, providing lifestyle advice and discussion of available treatments. The [NICE Clinical knowledge summary on erectile dysfunction](#) advises that all men who cannot be adequately managed in primary care should be referred to a specialist. The [European guidelines](#) recommend alprostadil as a second-line therapeutic option for men with ED. Alprostadil cream is an alternative route of administration to intracavernosal or intraurethral formulations. Some men may prefer this less-invasive option, but the fixed single dose may be a limitation in practice. Although direct comparison studies have not been reported, indirect comparisons suggest that alprostadil cream is generally less effective than PDE5 inhibitors and vacuum erection devices.

As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of alprostadil cream for erectile dysfunction. Alprostadil cream is slightly less costly than alprostadil for intracavernosal injection or intraurethral application, at usual therapeutic dose, but costs

substantially more than generic sildenafil.

The Department of Health has amended [regulations](#) to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction. Avanafil, tadalafil, vardenafil, branded sildenafil and alprostadil may be prescribed on the NHS only under certain circumstances (see individual preparations in the [British National Formulary](#)).

## Estimated usage

The [NHS prescription cost analysis for England 2013](#) reports that approximately 84,000 community prescriptions for alprostadil were dispensed in 2012 at a cost of approximately £5 million (net ingredient cost). 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 topical alprostadil cream (Takeda UK Ltd. Personal communication, August 2014). Specialists involved in the production of this evidence summary advise is that this is likely to be an overestimate because of the efficacy and side-effect profile of topical alprostadil cream and wider availability of generic sildenafil as a treatment option.

## Relevance to NICE guidance programmes

Topical alprostadil cream is not currently planned into any other NICE work programme. Several NICE guidelines make reference to the identification and management of erectile dysfunction. For example:

- [Management of multiple sclerosis in primary and secondary care](#) (NICE guideline CG186) advises that all people with multiple sclerosis should have a comprehensive review of their care at least once a year. Part of this review should include an assessment of sexual function.
- [Diagnosis and management of type 1 diabetes in children, young people and adults](#) (NICE guideline CG15) advises that men should be asked annually whether erectile dysfunction is an issue and treatment with a (PDE5) inhibitor should be offered if appropriate, and referral to a service offering management of erectile dysfunction should be discussed if PDE5 inhibitors are not successful. [An update of this guideline is in progress.](#)

- [Type 2 diabetes – newer agents \(partial update of CG66\)](#) (NICE guideline CG87) advises that the issue of erectile dysfunction should be reviewed annually in men with type 2 diabetes. A PDE5 inhibitor should be offered if appropriate and referral to a service offering management of erectile dysfunction should be discussed if PDE5 inhibitors are not successful. [An update of this guideline is in progress.](#)
- [MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction](#) (NICE guideline CG172) states that, when treating erectile dysfunction, treatment with a PDE5 inhibitor may be considered in men who have had an myocardial infarction more than 6 months earlier who are now stable.
- [Prostate cancer: diagnosis and treatment](#) (NICE guideline CG175) states that men with prostate cancer should have early and ongoing access to specialist erectile dysfunction services, including treatment with PDE5 inhibitors, and vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative.

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## Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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### Declarations of interest

Chris Chapple has acted as a paid consultant for AMS, Allergan, Astellas, Lilly, ONO, Pfizer and Recordati and as a researcher, trial participant and spoken on behalf of Allergan, Astellas, Pfizer and Recordati.

Mike Foster had no relevant interests to declare.

Ian Pearce had no relevant interests to declare.

### **About this evidence summary**

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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