



Erectile dysfunction: avanafil

Evidence summary

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www.nice.org.uk/guidance/esnm45

Key points from the evidence

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

Summary

Three [randomised controlled trials](#) (RCTs; total n=1334) have evaluated the phosphodiesterase type 5 (PDE5) inhibitor, avanafil, in men with erectile dysfunction in the general population ([Goldstein et al. 2012a](#)), with diabetes mellitus ([Goldstein et al. 2012b](#)), and post-prostatectomy ([Mulhall et al. 2013](#)). Overall, compared with placebo, they found that avanafil 50 mg, 100 mg and 200 mg statistically significantly improved the percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse; the percentage of sexual attempts in which vaginal penetration was achieved; and [International Index of Erectile Function](#) erectile function domain scores. The majority of adverse events seen in clinical studies were mild-moderate in severity and resulted in infrequent discontinuations (2.8% with avanafil 100 mg in [Goldstein et al. 2012a](#)). However, it is not known how the efficacy, tolerability and safety of avanafil

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compare with the other PDE5 inhibitors (sildenafil, tadalafil and vardenafil).

Effectiveness	Safety
<ul style="list-style-type: none"> • The mean percentage of attempts resulting in successful intercourse was: <ul style="list-style-type: none"> – 41.3%, 57.1%, and 57.0% for avanafil 50 mg, 100 mg, and 200 mg respectively in the general population with erectile dysfunction, compared with 27.0% for placebo (all $p \leq 0.0002$; Goldstein et al. 2012a). – 34.4% and 40.0% for avanafil 100 mg and 200 mg respectively in men with diabetes (89.5% type 2), compared with 20.5% for placebo (both $p < 0.0001$; Goldstein et al. 2012b). – 23.4% and 26.4% for avanafil 100 mg and 200 mg respectively in men post-prostatectomy, compared with 8.9% for placebo (both $p \leq 0.0004$; Mulhall et al. 2013). • There are no direct head-to-head comparisons of PDE5 inhibitors and indirect comparisons are limited by differences in study design 	<ul style="list-style-type: none"> • Across the 3 RCTs, adverse events were reported in around 30–40% taking avanafil and around 25% of men taking placebo (no statistical analyses reported). • The summary of product characteristics states that the most common adverse events reported in clinical studies (n=2144) were headache, flushing, nasal and sinus congestion (all with an incidence of between 1 in 10 and 1 in 100), and back pain (incidence between 1 in 100 and 1 in 1000). • Men should be aware of how they react to avanafil before driving or using machines because dizziness, somnolence and altered vision were reported in clinical studies (incidence between 1 in 100 and 1 in 1000).

<ul style="list-style-type: none">• According to <u>European guidelines on male sexual dysfunction</u>, erections sufficient for intercourse have been reported in 60–80% of men taking sildenafil, tadalafil and vardenafil.	
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User factors	Resource implications
<ul style="list-style-type: none"> • European guidelines advise that the choice of PDE5 inhibitor depends on the frequency of intercourse and the man's personal experience of these drugs. • According to the summary of product characteristics, avanafil has similar contraindications, cautions and interactions to other PDE5 inhibitors. • Avanafil, tadalafil, sildenafil and vardenafil are taken on-demand. At lower doses, tadalafil is also licensed to be taken daily. • According to the summaries of product characteristics, sildenafil should be taken 1 hour before sexual activity, whereas avanafil, tadalafil and vardenafil should be taken 25–30 minutes before sexual activity. 	<ul style="list-style-type: none"> • When usual starting doses are considered, avanafil costs significantly more than generic sildenafil (£14.08 for 4 x 100 mg tablets compared with £1.08 for 4 x 50 mg tablets). • It is competitively priced compared with on-demand tadalafil (£26.99 for 4 x 10 mg tablets) and vardenafil (£17.88 for 4 x 10 mg tablets). • 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 only be prescribed on the NHS under certain circumstances (see individual preparations in the British National Formulary).

Introduction and current guidance

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. Although erectile dysfunction is a benign disorder, it affects physical and psychosocial health and has a significant impact on the quality of life of sufferers and their partners.

Erectile dysfunction can generally be treated successfully, although it often cannot be cured. Regardless of the cause, the [European guidelines](#) advise that first-line therapy is usually oral treatment with selective PDE5 inhibitors (sildenafil, tadalafil and vardenafil).

The NICE guidelines on [multiple sclerosis](#) (NICE clinical guideline 8), [type 1 diabetes](#) (NICE clinical guideline 15), [type 2 diabetes](#) (NICE clinical guideline 87) and [myocardial infarction](#) (NICE clinical guideline 172) advise that men with erectile dysfunction should be offered PDE5 inhibitors. Men with [prostate cancer](#) should have early and ongoing access to specialist erectile dysfunction services (NICE clinical guideline 175) (see [Relevance to NICE guidance programmes](#) for more information).

This evidence summary considers the efficacy and safety of avanafil, a new PDE5 inhibitor.

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

Product overview

Avanafil ([Spedra, A. Menarini Farmaceutica Internazionale](#)) received a European marketing authorisation for the treatment of erectile dysfunction in adult men in June 2013 and was launched in the UK in March 2014.

The recommended dose of avanafil is 100 mg as needed approximately 30 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. As with other PDE5 inhibitors, sexual stimulation is required for a response to treatment.

According to the [summary of product characteristics](#), avanafil has similar contraindications, cautions and interactions to other PDE5 inhibitors.

[Full text of Product overview.](#)

Evidence review

- This evidence summary is based on 4 phase III studies that have evaluated the efficacy and safety of avanafil in men with erectile dysfunction. Three of the studies are double-blind, [RCTs](#) of 12 weeks' duration (1 in a general population with erectile dysfunction [without diabetes or post-prostatectomy; [Goldstein et al. 2012a](#), n=646]; 1

in men with type 1 or type 2 diabetes [[Goldstein et al. 2012b](#), n=390] and 1 in men with erectile dysfunction following bilateral nerve-sparing radical prostatectomy [[Mulhall et al. 2013](#), n=298]. Men were instructed to take placebo or avanafil 50 mg ([Goldstein et al. 2012a](#) only), 100 mg or 200 mg as needed approximately 30 minutes before initiation of sexual activity.

- In addition, 712 men from 2 of the RCTs ([Goldstein et al. 2012a](#) and [Goldstein et al. 2012b](#)) enrolled in a 52-week open-label extension study ([Belkoff et al. 2013](#)). All men were initially assigned to avanafil 100 mg but could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based on their individual response to treatment.
- Overall, in the 3 RCTs, compared with placebo, avanafil 50 mg, 100 mg and 200 mg statistically significantly improved all 3 co-primary outcomes (percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse; percentage of sexual attempts in which vaginal penetration was achieved; and [International Index of Erectile Function](#) erectile function domain scores). The mean percentage of attempts resulting in successful intercourse was:
 - 41.3%, 57.1%, and 57.0% for avanafil 50 mg, 100 mg, and 200 mg respectively in the general population with erectile dysfunction, compared with 27.0% for placebo (all $p < 0.0002$; [Goldstein et al. 2012a](#))
 - 34.4% and 40.0% for avanafil 100 mg and 200 mg respectively in men with diabetes (89.5% type 2), compared with 20.5% for placebo (both $p < 0.0001$; [Goldstein et al. 2012b](#))
 - 23.4% and 26.4% for avanafil 100 mg and 200 mg respectively in men post-prostatectomy, compared with 8.9% for placebo (both $p \leq 0.0004$; [Mulhall et al. 2013](#)).

Avanafil 100 mg and 200 mg were statistically significantly better than avanafil 50 mg ([Goldstein et al. 2012a](#)) but there were no significant differences between avanafil 100 mg and 200 mg ([Goldstein et al. 2012a](#) and [Goldstein et al. 2012b](#); comparison not reported in [Mulhall et al. 2013](#)).

- Higher response rates were generally seen with avanafil in the general population with erectile dysfunction, than in men with diabetes or post-prostatectomy. In the latter 2 populations, some improvements were of borderline clinical importance only. According to the [European public assessment report for avanafil](#), response rates

generally decreased as the severity of erectile dysfunction increased.

- The open-label long-term extension study suggests that the effects of avanafil are maintained for up to 52 weeks. In this study, about two-thirds of men responded to avanafil 100 mg and, of those who did not, a further two-thirds responded to 200 mg. However, only 24.0% of men remained on the 100 mg dose, with 75.3% of men voluntarily increasing their dose to 200mg ([Belkoff et al. 2013](#)).
- From the studies, the overall safety profile of avanafil appears to be similar to that of other PDE5 inhibitors and no new safety concerns have been raised. The majority of adverse events seen in clinical studies were mild-moderate in severity and resulted in infrequent discontinuations (2.8% with avanafil 100 mg in [Goldstein et al. 2012a](#); [European public assessment report for avanafil, 2013](#)).
- The [summary of product characteristics](#) states that the most common adverse events reported in clinical studies (n=2144) were headache, flushing, nasal and sinus congestion (all with an incidence of between 1 in 10 and 1 in 100), and back pain (incidence between 1 in 100 and 1 in 1000). Men should be aware of how they react to avanafil before driving or using machines because dizziness, somnolence and altered vision were reported in clinical studies with avanafil (incidence between 1 in 100 and 1 in 1000).
- The 3 RCTs are placebo-controlled and it is not known how avanafil compares to other PDE5 inhibitors. Limitations of the open-label extension study include the lack of a comparator and blinding, and the possibility that responders to avanafil in the qualifying studies may have been more likely to enrol than non-responders, potentially over estimating the benefits of avanafil.

[Full text of Evidence review.](#)

Context

Alternative PDE5 inhibitors to avanafil are sildenafil, tadalafil and vardenafil. The [European guidelines on male sexual dysfunction](#) state that the choice of PDE5 inhibitor depends on the frequency of intercourse (occasional or 3–4 times weekly) and the man's personal experience of these drugs. All 4 PDE5 inhibitors are taken on-demand. At lower doses, tadalafil is also licensed to be taken daily, providing an alternative to on-demand dosing for couples who prefer spontaneous rather than scheduled sexual activity or who have frequent sexual activity.

When usual starting doses are considered, avanafil costs significantly more than generic sildenafil (£14.08 for 4 x 100 mg tablets compared with £1.08 for 4 x 50 mg tablets) but is competitively priced compared with on-demand tadalafil (£26.99 for 4 x 10 mg tablets) and vardenafil (£17.88 for 4 x 10 mg tablets).

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 only be prescribed on the NHS under certain circumstances (see individual preparations in the [British National Formulary](#)).

[Full text of Context.](#)

Estimated impact for the NHS

Although avanafil was statistically significantly more effective than placebo and well tolerated in the studies, it is not known how its efficacy, safety and tolerability compare with sildenafil, tadalafil and vardenafil. There are no direct head-to-head comparisons and indirect comparisons are limited by differences between the studies (for example, study designs, populations, outcomes, rating scales and definitions of success). According to the [European guidelines on male sexual dysfunction](#), efficacy rates (erection rigidity sufficient for vaginal penetration) are:

- 56%, 77% and 84% in men taking 25 mg, 50 mg and 100 mg of sildenafil, respectively.
- 67% and 81% in men taking 10 mg and 20 mg of tadalafil, respectively.
- 66%, 76% and 80% in men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively.

It is also not possible to draw conclusions around the efficacy and tolerability of avanafil in men whose erectile dysfunction has consistently not responded to the other PDE5 inhibitors, or whether it is tolerated by men who have experienced dose-limiting adverse effects with another of these drugs, because these men were excluded from studies.

As well as efficacy, safety and cost, local decision makers will need to take individual user factors into account when considering the likely place in therapy of avanafil for erectile dysfunction. The [European guidelines](#) advise that the choice of PDE5 inhibitor depends on the frequency of intercourse and the man's personal experience of these drugs. Onset of action might be important to some men taking PDE5 inhibitors on-demand. According to

the [summaries of product characteristics](#), sildenafil should be taken 1 hour before sexual activity, whereas avanafil, tadalafil and vardenafil should be taken 25–30 minutes before sexual activity.

The current [marketing authorisation](#) states that avanafil should be taken approximately 30 minutes before sexual activity. However, the manufacturer, Menarini, has advised that a licence variation to examine the therapeutic effect of avanafil approximately 15 minutes after dosing in men with mild to severe erectile dysfunction has been submitted to the [European Medicines Agency](#). A decision is expected later in 2014 (Menarini; personal communication, June 2014). Any new evidence on a 15 minute effectiveness window will need to be assessed before any recommendations can be made in this regard.

The manufacturer of avanafil estimates that about 5000 men might be prescribed avanafil second-line in the UK at any one time (Menarini; personal communication, March 2014). However, specialists involved in the production of this evidence summary have advised that this might be an overestimation, primarily due to the increasing impact of generic sildenafil.

[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

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. Although erectile dysfunction is a benign disorder, it affects physical and psychosocial health and has a significant impact on the

quality of life of sufferers and their partners.

Erectile dysfunction is common. According to the [European guidelines](#), in an American study, 52% of men aged 40–70 years of age reported some degree of erectile dysfunction. The prevalence increases in older men and the severity increases with aging. In a German study, the prevalence of erectile dysfunction in men aged 30–80 years was 19.2%, with a steep age-related increase from 2.3% to 53.4%

Erectile dysfunction is a symptom and not a disease, therefore it is important to identify any underlying disease or condition that may be causing it. Erectile dysfunction 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 ([NICE Clinical knowledge summary: erectile dysfunction](#)).

Erectile dysfunction shares common risk factors with cardiovascular disease (for example, lack of exercise, obesity, smoking, hypercholesterolaemia, and metabolic syndrome) and, according to the [European guidelines](#), there is increasing evidence that erectile dysfunction can be an early manifestation of coronary artery and peripheral vascular disease. The risk of erectile dysfunction may be reduced by modifying these risk factors and all men with erectile dysfunction should receive appropriate counselling on risk reduction and lifestyle modification, particularly taking exercise or losing weight.

Erectile dysfunction can generally be treated successfully, although it often cannot be cured. Consideration should be given to substituting medication that might cause erectile dysfunction ([NICE Clinical knowledge summary: erectile dysfunction](#)). Regardless of the cause, the [European guidelines](#) advise that first-line therapy is usually oral treatment with selective phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil), assuming there are no contraindications or drug interactions. PDE5 inhibitors are not initiators of erection and require sexual stimulation for an erection to occur.

No data are available from double- or triple-blind multicentre studies comparing the efficacy of, or men's preference for sildenafil, tadalafil, and vardenafil. The [European guidelines](#) state that the choice of PDE5 inhibitor depends on the frequency of intercourse (occasional or 3–4 times weekly) and the man's personal experience of these drugs. Men should be advised whether a drug is short- or long-acting, about any possible disadvantages, and how to use the drug. Daily tadalafil provides an alternative to on-demand dosing for couples who prefer spontaneous rather than scheduled sexual

activity or who have frequent sexual activity ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)).

NICE has not published a clinical guideline on erectile dysfunction, although several published NICE guidelines do make recommendations around identifying and managing erectile dysfunction in specific patient groups (see [Relevance to NICE guidance programmes](#) for more information). PDE5 inhibitors should be offered to men with erectile dysfunction and [multiple sclerosis](#) (NICE clinical guideline 8), [type 1 diabetes](#) (NICE clinical guideline 15) or [type 2 diabetes](#) (NICE clinical guideline 87), or who have had an [myocardial infarction](#) more than 6 months earlier who are now stable (NICE clinical guideline 172). Men with [prostate cancer](#) should have early and ongoing access to specialist erectile dysfunction services (NICE clinical guideline 175).

Other treatment options include vacuum erection devices and intracavernous, intraurethral and topical alprostadil. Surgical implantation of a penile prosthesis may be considered in men who fail pharmacotherapy or who want a permanent solution ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)).

The majority of drug treatments for erectile dysfunction may only be prescribed on the NHS under certain circumstances (see individual preparations in the [British National Formulary](#)). In addition, the Department of Health [recommends](#) that treatment should also be available from specialist services when the condition is causing severe distress.

Following a [consultation](#), the Department of Health has amended the [regulations](#) to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction. This evidence summary considers the efficacy and safety of avanafil, a new PDE5 inhibitor. Avanafil has been added to the list of treatments for erectile dysfunction that are still restricted including tadalafil, vardenafil, branded sildenafil and alprostadil.

Product overview

Drug action

Avanafil ([Spedra, A. Menarini Farmaceutica Internazionale](#)) is a reversible inhibitor of cyclic guanosine monophosphate (cGMP) -specific PDE5 inhibitor. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle

relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation ([summary of product characteristics for avanafil, 2014](#)).

Licensed therapeutic indication

Avanafil ([Spedra](#)) received a European marketing authorisation for the treatment of erectile dysfunction in adult men in June 2013 and was launched in the UK in March 2014.

The current [marketing authorisation](#) states that avanafil should be taken approximately 30 minutes before sexual activity. However, the manufacturer, Menarini, has advised that a licence variation to examine the therapeutic effect of avanafil approximately 15 minutes after dosing in men with mild to severe erectile dysfunction has been submitted to the [European Medicines Agency](#). A decision is expected later in 2014 (Menarini; personal communication, June 2014). Any new evidence on a 15 minute effectiveness window will need to be assessed before any recommendations can be made in this regard.

According to the [summary of product characteristics](#), avanafil has similar contraindications, cautions and interactions to other PDE5 inhibitors. It is [contraindicated](#) in men:

- taking nitrates.
- in whom vasodilation or sexual activity are inadvisable.
- with hypotension (resting blood pressure below 90/50 mmHg) or hypertension (resting blood pressure > 170/100 mmHg); stroke, myocardial infarction, life-threatening arrhythmia within the previous 6 months; unstable angina and congestive heart failure New York Heart Association class 2 or greater.
- with severe hepatic or renal impairment.
- with a previous history of non-arteritic anterior ischaemic optic neuropathy or known hereditary degenerative retinal disorders.

[Special warnings and precautions for use](#) include cardiovascular disease; priapism; visual, bleeding and hearing disorders; and concomitant use of alpha-blockers, antihypertensive drugs, alcohol, and other treatments for erectile dysfunction. Co-administration of avanafil with potent inhibitors of CYP3A4, such as ketoconazole, clarithromycin or ritonavir, is contraindicated. See the [summary of product characteristics for avanafil](#) for full details.

Course and cost

Avanafil is available as 50 mg, 100 mg or 200 mg tablets. The recommended dose is 100 mg as needed approximately 30 minutes before sexual activity. If it is taken with food, the onset of activity may be delayed. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once daily. Sexual stimulation is required for a response to treatment.

According to [MIMS](#) (June 2014; costs excluding VAT):

- avanafil 50 mg tablets cost £10.94 for 4 and £19.70 for 8.
- avanafil 100 mg tablets cost £14.08 for 4 and £26.26 for 8.
- avanafil 200 mg tablets cost £21.90 for 4 and £39.40 for 8.

Evidence review

This evidence summary is based on 4 phase III studies that have evaluated the efficacy and safety of avanafil in men with erectile dysfunction. Three of the studies are 12-week [randomised controlled trials](#) (RCTs; 1 in a general population [[Goldstein et al. 2012a](#)]; 1 in men with type 1 or type 2 diabetes mellitus [[Goldstein et al. 2012b](#)]; and 1 in men who had undergone bilateral nerve-sparing radical prostatectomy [[Mulhall et al. 2013](#)]). The designs of these 3 studies are similar and they are described together. The fourth study is a 52-week open-label extension study ([Belkoff et al. 2013](#)).

Another phase III study ([Zhao et al. 2012](#)) evaluating the efficacy and safety of avanafil for treating erectile dysfunction was identified but has not been discussed in this evidence summary because it was undertaken in Korea, included a general population of only 208 men, and comes to similar conclusions to the larger study in a general population that has been discussed ([Goldstein et al. 2012a](#)).

Information from the studies has been supplemented and clarified using the [European public assessment report for avanafil](#).

RCTs evaluating the safety and efficacy of avanafil in men with erectile dysfunction in the general population ([Goldstein et al. 2012a](#)), with diabetes mellitus ([Goldstein et al. 2012b](#)), and post-prostatectomy ([Mulhall et al. 2013](#))

- Design: all 3 studies were randomised, double-blind, placebo-controlled, 12-week, parallel-design studies undertaken in multiple centres in the US (Goldstein et al. 2012a, n=646: Goldstein et al. 2012b, n=390: Mulhall et al. 2013, n=298).
- Population: the studies enrolled men aged 18 years or older (mean age 56–58 years) with mild to severe erectile dysfunction of at least 6 months duration who had been in a monogamous, heterosexual relationship for at least 3 months. Erectile dysfunction was defined as the inability to achieve vaginal penetration on at least 50% of attempts at sexual intercourse without the use of medical therapy. Men agreed to make at least 4 attempts at intercourse per month and not to use any other treatments for erectile dysfunction during the study. Men with diabetes mellitus (89.5% type 2) or who had undergone bilateral nerve-sparing radical prostatectomy for localised prostate cancer (staging pT2 or less and Gleason score 7 or less) were studied separately (Goldstein et al. 2012b and Mulhall et al. 2013, respectively) from those in the general population (Goldstein et al. 2012a) because the response to treatments for erectile dysfunction may differ in these populations.
- Exclusion criteria: all 3 studies excluded men with cardiovascular illness within the preceding 6 months (including myocardial infarction, stroke, high-risk arrhythmia, unstable angina and congestive heart failure); uncontrolled hypertension or hypotension; retinitis pigmentosa or non-arteritic anterior ischemic optic neuropathy; abnormal liver function tests or severe renal failure; and treatment with nitrates, CYP3A4 inhibitors or anti-androgens. Men in whom erectile dysfunction previously consistently failed to respond, or who experienced dose-limiting adverse effects with a PDE5 inhibitor were also excluded. In Goldstein et al. (2012b), men with uncontrolled diabetes were excluded. In Mulhall et al. (2013), men with a history of previous pelvic surgery, brachytherapy, or cryotherapy of the prostate; or a history of severe erectile dysfunction requiring routine medical therapy prior to bilateral nerve-sparing radical prostatectomy were excluded.
- Follow-up: in all 3 studies, a 4-week baseline period without treatment for erectile dysfunction was followed by a 12-week treatment period. Men who met the initial eligibility criteria entered the 4-week, non-treatment run-in period and were instructed to record information on each of their attempts at sexual intercourse. At the end of the run-in period, they were eligible for randomisation to treatment if they:
 - documented at least 4 attempts at sexual intercourse during the run-in period
 - failed to maintain an erection of sufficient duration to enable successful intercourse for at least 50% of their attempts

- had an International Index of Erectile Function (IIEF) erectile function domain score of 5 to 25.

The IIEF is a 15-item questionnaire, self-administered measure of erectile function. The 15 items cover 5 domains: erectile function (6 items), orgasmic function (2 items), sexual desire (2 items), intercourse satisfaction (3 items), and overall sexual satisfaction (2 items). This questionnaire was completed at each 4-weekly study visit. Throughout the study, men completed diaries recording when medication was used, when sexual activity was initiated, and answering Sexual Encounter Profile questions.

- Intervention and comparison: eligible men were randomised to placebo or different doses of avanafil (50 mg or 100 mg or 200 mg in Goldstein et al. 2012a and 100 mg or 200 mg in Goldstein et al. 2012b and Mulhall et al. 2013) to be taken on-demand, approximately 30 minutes before sexual activity. The method of allocation described suggests that this was concealed. Up to 2 doses of study drug could be taken in a 24-hour period at least 12 hours apart. Baseline characteristics were similar across treatment groups in the studies.
- Outcomes: 3 co-primary efficacy outcomes were used in the studies:
 - change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which men were able to maintain an erection of sufficient duration to enable successful intercourse (question 3 of the Sexual Encounter Profile: 'Did your erection last long enough for you to have successful intercourse?')
 - change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which men were able to insert the penis into the partner's vagina (question 2 of the Sexual Encounter Profile: 'Were you able to insert your penis into your partner's vagina?')
 - change in the IIEF erectile function domain score from baseline to the end of the 12-week treatment period.

Adverse events and vital signs were monitored at each study visit.

The Committee for Medicinal Products for Human Use (CHMP) found that there was no pre-planned definition of 'responders' and 'clinically significant' change from baseline for the 3 co-primary endpoints. Therefore, a post-hoc analysis was provided for the CHMP

assessment of avanafil, which defined the minimum thresholds for clinically relevant changes from baseline for successful intercourse, vaginal penetration and IIEF as improvements of 23%, 21% and more than 4 points respectively ([European public assessment report for avanafil, 2013](#)).

Table 1 Summary of RCTs in men with erectile dysfunction in the general population ([Goldstein et al. 2012a](#)), with diabetes mellitus ([Goldstein et al. 2012b](#)), and post-prostatectomy ([Mulhall et al. 2013](#))

		Placebo	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg	Analysis
Randomised	General population	n=162	n=161	n=161	n=162	
	Diabetes	n=130	NA	n=129	n=131	
	Post-prostatectomy	n=100	NA	n=99	n=99	
Efficacy^a	General population	n=155	n=154	n=157	n=156	
	Diabetes	n=127 ^b and n=125 ^c	NA	n=126 ^b and n=125 ^c	n=126 ^b and n=125 ^c	
	Post-prostatectomy	n=96	NA	n=94	n=96	
Primary outcome 1: mean % change in sexual attempts in which men were able to maintain an erection of sufficient duration to have successful intercourse over 12 weeks	General population	14.4% increase (from 12.6% to 27.0%)	27.8% increase (from 13.5% to 41.3%)	43.2% increase (from 13.9% to 57.1%)	44.6% increase (from 12.4% to 57.0%)	Comparisons with placebo: all $p \leq 0.0002$ 50 mg versus 100 mg and 200 mg: both $p < 0.0001$ 100 mg versus 200 mg: NS

	Diabetes	10.5% increase (from 10.0% to 20.5%)	NA	26.2% increase (from 8.2% to 34.4%)	32% increase (from 8.0% to 40.0%)	Comparisons with placebo: both $p < 0.0001$ 100 mg versus 200 mg: NS
	Post-prostatectomy ^d	4.8% increase (from 4.1% to 8.9%)	NA	18.3% increase (from 5.1% to 23.4%)	21.1% increase (from 5.3% to 26.4%)	Comparisons with placebo: $p = 0.0004$ and $p < 0.0001$ for 100 mg and 200 mg respectively Statistical analysis for 100 mg versus 200 mg not reported

Primary outcome 2: Mean % change in sexual attempts in which men were able to insert the penis into the partner's vagina over 12 weeks	General population	7.1% increase (from 46.7% to 53.8%)	18.9% increase (from 45.4% to 64.3%)	27.3% increase (from 46.6% to 73.9%)	29.0% increase (from 48.3% to 77.3%)	Comparisons with placebo: all $p \leq 0.0009$ 50 mg versus 100 mg: $p = 0.0064$ 50 mg versus 200 mg: and $p = 0.0004$ 100 mg versus 200 mg: NS
	Diabetes	6.0% increase (from 36.0% to 42.0%)	NA	21.5% increase (from 32.5% to 54.0%)	22.0% increase (from 41.5% to 63.5%)	Comparisons with placebo: $p = 0.0004$ and $p < 0.0001$ for 100 mg and 200 mg respectively 100 mg versus 200 mg: NS

	Post-prostatectomy ^d	0.4% decrease (from 20.1% to 19.7%)	NA	15.3% increase (from 17.2% to 32.5%)	20.9% increase (from 19.9% to 40.8%)	Comparisons with placebo: p=0.0003 and p<0.0001 for 100 mg and 200 mg respectively Statistical analysis for 100 mg versus 200 mg not reported
Primary outcome 3: Mean change in the IIEF erectile function domain score over 12 weeks	General population	2.9 increase (from 12.4 to 15.3)	5.5 increase (from 12.6 to 18.1)	8.3 increase (from 12.6 to 20.9)	9.4 increase (from 12.8 to 22.2)	Comparisons with placebo: all p≤0.0014 50 mg versus 100 mg: p<0.0001 50 mg versus 200 mg: p=0.0003 100 mg versus 200 mg: NS

	Diabetes	1.8 increase (from 11.4 to 13.2)	NA	4.6 increase (from 11.2 to 15.8)	5.3 increase (from 12.0 to 17.3)	Comparisons with placebo: p=0.0017 and p<0.0001 for 100 mg and 200 mg respectively 100 mg versus 200 mg: NS
	Post-prostatectomy ^d	0.2 increase (from 9.1 to 9.3)	NA	3.5 increase (from 9.1 to 12.6)	5.2 increase (from 9.5 to 14.7)	Comparisons with placebo: p=0.0001 and p<0.0001 for 100 mg and 200 mg respectively Statistical analysis for 100 mg versus 200 mg not reported
Safety^e	General population	n=161	n=160	n=161	n=162	
	Diabetes	n=130	NA	n=127	n=131	
	Post-prostatectomy	n=100	NA	n=99	n=99	
Men reporting adverse events	General population	42/161 (26.1%)	52/160 (32.5%)	68/161 (42.2%)	63/162 (38.9%)	No statistical analyses reported
	Diabetes	31/130 (23.8%)	NA	45/127 (35.4%)	42/131 (32.1%)	

	Post-prostatectomy	23/100 (23.0%)	NA	38/99 (38.4%)	45/99 (45.5%)	
Interruptions or discontinuations due to adverse events	General population	5/161 (3.1%)	3/160 (1.9%)	6/161 (3.7%)	4/162 (2.5%)	No statistical analyses reported
	Diabetes	0 (0%)	NA	1/127 (0.8%)	2/131 (1.5%)	
	Post-prostatectomy	1/100 (1.0%)	NA	2/99 (2.0%)	2/99 (2.0%)	

Abbreviations: IIEF, International Index of Erectile Function; ITT, intention-to-treat; NA, not applicable; NS, not statistically significant; p, p value.

^a 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. The last observation carried forward convention was used to adjust for missing data.

^b ITT population for the first 2 primary outcomes.

^c ITT population for the third primary outcome.

^d Data have primarily been taken from the published papers and are supplemented with information from the European public assessment report (EPAR) for avanafil. Efficacy data for post-prostatectomy are primarily taken from the EPAR because this data was incompletely reported in the paper.

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

Open-label long-term extension study evaluating the safety and efficacy of avanafil in men with erectile dysfunction (Belkoff et al. 2013)

- Design: this study was an open-label extension study with a 52-week treatment period.
- Population: The study included 712 men (mean age 56 years) with (32%) and without diabetes who had completed the 12-week studies by Goldstein et al. (2012a) and Goldstein et al. (2012b). As in the RCTs, men were requested to make at least 4 attempts per month at sexual intercourse and for each attempt, they were instructed to record information regarding the administration of study drug and sexual experience in a subject diary. Allowed and prohibited medications the same as those

in the RCTs.

- Intervention and comparison: all men were initially assigned to treatment with avanafil 100 mg (regardless of the dose taken during the qualifying study) but could request a dose increase to 200 mg (for increased efficacy) or dose decrease to 50 mg (for improved tolerability). As in the RCTs, men were instructed to take 1 dose of study drug approximately 30 minutes before initiating sexual activity and could take up to 2 doses in 24 hours. The mean treatment duration was 35.3 weeks: 21.5% (153/712) of men took avanafil for at least 52 weeks.
- Outcomes: the same 3 co-primary efficacy outcomes were used as in the RCTs, but with a 52-week, rather than 12-week treatment period.

Table 2 Summary of open-label long-term study evaluating the safety and efficacy of avanafil in men with erectile dysfunction (Belkoff et al. 2013)

	Avanafil 100 mg only	Avanafil 100 mg and 200 mg	Total population	Analysis
Randomised	n=171	n=536	n=712 ^a	
Efficacy^b	n=147	n=535	n=686	
Primary outcome 1: mean % change in sexual attempts in which men were able to maintain an erection of sufficient duration to have successful intercourse over 52 weeks	54.4% increase (from 13.3% to 67.7%)	54.9% increase (from 11.4% to 66.3%)	54.8% increase (from 11.8% to 66.6%)	No statistical analyses reported
Primary outcome 2: Mean % change in sexual attempts in which men were able to insert the penis into the partner's vagina over 52 weeks	39.2% increase (from 44.1% to 83.3%)	36.4% increase (from 43.0% to 79.4%)	36.9% increase (from 43.3% to 80.2%)	No statistical analyses reported

Primary outcome 3: Mean change in the IIEF erectile function domain score over 52 weeks	8.6 increase (from 13.6 to 22.2)	10.8 increase (from 11.9 to 22.7)	10.3 increase (from 12.3 to 22.6)	No statistical analyses reported
	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg	Analysis
Safety^c	n=4	n=711	n=514	
Men reporting adverse events	3/4 (75.0%)	135/711 (19.0%)	183/514 (35.6%)	No statistical analyses reported
Interruptions or discontinuations due to adverse events	1/4 (25.0%)	13/711 (1.8%)	6/514 (1.2%)	No statistical analyses reported
<p>Abbreviations: IIEF, <u>International Index of Erectile Function</u>; ITT, <u>intention-to-treat</u>;</p> <p>^a 3 men requested a dose decrease, 1 man received all 3 doses and 1 man did not receive any study drug.</p> <p>^b 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. The last observation carried forward convention was used to adjust for missing data.</p> <p>^c Safety analyses included all men who from the 12-week studies who signed informed consent.</p>				

Clinical effectiveness

Overall, in the 3 RCTs, ([Goldstein et al. 2012a](#), [Goldstein et al. 2012b](#) and [Mulhall et al. 2013](#)), avanafil 50 mg, 100 mg and 200 mg statistically significantly improved the percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse; the percentage of sexual attempts in which vaginal penetration was achieved; and IIEF erectile function domain scores compared with placebo. In [Goldstein et al. \(2012a\)](#), avanafil 100 mg and 200 mg were statistically significantly better than avanafil 50 mg. In [Goldstein et al. 2012a](#) and [Goldstein et al.](#)

[2012b](#), there were no significant differences between avanafil 100 mg and 200 mg (comparison not reported in [Mulhall et al. 2013](#)).

Higher response rates were generally seen with avanafil in the general population with erectile dysfunction ([Goldstein et al. 2012a](#)), than in men with diabetes (89.5% type 2; [Goldstein et al. 2012b](#)) or in men who had undergone bilateral nerve-sparing radical prostatectomy ([Mulhall et al. 2013](#)). In the latter 2 populations, some improvements were of borderline clinical importance only. According to the European public assessment report for avanafil, response rates generally decreased as the severity of erectile dysfunction increased.

The open-label long-term extension study suggests that the effects of avanafil are maintained for up to 52 weeks. In this study, about two-thirds of men experienced a response to avanafil 100 mg and, of those who did not, a further two-thirds experienced a response to 200 mg. However, only 24.0% of men remained on the 100 mg dose, with 75.3% of men voluntarily increasing their dose to 200mg ([Belkoff et al. 2013](#)).

General population with erectile dysfunction ([Goldstein et al. 2012a](#))

In this study, from baseline, placebo and avanafil 50 mg, 100 mg and 200 mg statistically significantly improved:

- successful intercourse (mean increase 14.4%, 27.8%, 43.2% and 44.6% respectively; all $p < 0.0001$).
- vaginal penetration (mean increase 7.1%, 18.9%, 27.3% and 29.0% respectively; all $p \leq 0.0025$).
- IIEF erectile function domain score (mean increase 2.9, 5.5, 8.3 and 9.4 respectively; all $p < 0.0001$).

Clinically important improvements from baseline are reported to be 23% for successful intercourse, 21% for vaginal penetration and 4 points for IIEF ([European public assessment report for avanafil](#)).

The mean percentage of sexual attempts resulting in successful intercourse was 41.3%, 57.1%, and 57.0% for avanafil 50 mg, 100 mg, and 200 mg respectively, compared with 27.0% for placebo. All doses of avanafil were statistically significantly more effective than placebo (all $p \leq 0.0002$ for successful intercourse, $p \leq 0.0009$ for vaginal penetration, and

$p \leq 0.0014$ for IIEF erectile function domain score). Avanafil 100 mg and 200 mg were statistically significantly better than avanafil 50 mg (both $p < 0.0001$ for successful intercourse, $p = 0.0004$ and $p = 0.0064$ respectively for vaginal penetration, and $p < 0.0001$ and $p = 0.0003$ respectively for IIEF erectile function domain score). However, there were no statistically significant differences between avanafil 100 mg and 200 mg. See table 1 for more details.

Type 1 or type 2 diabetes mellitus (Goldstein et al. 2012b)

In this study, in which 89.5% of men had type 2 diabetes, from baseline, placebo and avanafil 100 mg and 200 mg statistically significantly improved:

- successful intercourse (mean increase 10.5%, 26.2% and 32.0% respectively; all $p < 0.0001$).
- vaginal penetration (mean increase 6.0%, 21.5% and 22.0% respectively; all $p \leq 0.0088$).
- IIEF erectile function domain score (mean increase 1.8, 4.6 and 5.3; all $p \leq 0.0066$).

The mean percentage of sexual attempts resulting in successful intercourse was 34.4% and 40.0% for avanafil 100 mg and 200 mg respectively, compared with 20.5% for placebo. Both doses of avanafil were statistically significantly more effective than placebo (both $p < 0.0001$ for successful intercourse, $p \leq 0.0004$ for vaginal penetration, and $p \leq 0.0017$ for IIEF erectile function domain score). However, there were no statistically significant differences between avanafil 100 mg and 200 mg. See table 1 for more details.

Bilateral nerve-sparing radical prostatectomy (Mulhall et al. 2013)

In this study, from baseline, placebo and avanafil 100 mg and 200 mg statistically significantly improved:

- successful intercourse (mean increase 4.8%, 18.3% and 21.1% respectively; all $p < 0.0001$).
- vaginal penetration (mean increase -0.4%, 15.3% and 20.9% respectively; no significant difference seen with placebo, $p < 0.0001$ for both doses of avanafil).
- IIEF erectile function domain score (mean increase 0.2, 3.5 and 5.2; no significant difference seen with placebo, $p < 0.0001$ for both doses of avanafil).

The mean percentage of sexual attempts resulting in successful intercourse was 23.4% and 26.4% for avanafil 100 mg and 200 mg respectively, compared with 8.9% for placebo. Both doses of avanafil were statistically significantly more effective than placebo (both $p \leq 0.0004$ for successful intercourse, $p \leq 0.0003$ for vaginal penetration, and $p \leq 0.0001$ for IIEF erectile function domain score). Avanafil 100 mg and 200 mg were not compared in this study. See table 1 for more details.

Open-label long-term extension study ([Belkoff et al. 2013](#))

Overall, during the 52-week treatment period (mean treatment duration 35.3 weeks), the mean percentage of sexual attempts resulting in successful intercourse was:

- 66.6% in the total population (mean change from baseline 54.8%).
- 67.7% in men who received avanafil 100 mg only (mean change from baseline 54.4%).
- 66.3% in men who received avanafil 100 mg and 200 mg (67.7% mean change from baseline 54.9%). Men in this group had higher mean IIEF erectile function domain scores at baseline than those who received 100 mg only, indicating a greater degree of erectile dysfunction ([European public assessment report for avanafil, 2013](#)).

Overall, the mean percentage of sexual attempts resulting in successful vaginal penetration was 80.2% during the 52-week treatment period (mean change from baseline 36.9%) and the mean IIEF erectile function domain score was 22.6 at the end of treatment (mean change in score from baseline 10.3). The data suggest that increasing the dose of avanafil to 200 mg may improve efficacy in some men who do not experience a response to 100 mg. See table 2 for more information.

Safety and tolerability

The overall safety profile of avanafil appears to be similar to that of other PDE5 inhibitors and no new safety concerns have been raised. The majority of adverse events seen in clinical studies were mild-moderate in severity and resulted in infrequent discontinuations (2.8% with avanafil 100 mg in [Goldstein et al. 2012a](#); [European public assessment report for avanafil, 2013](#)).

General population with erectile dysfunction ([Goldstein et al. 2012a](#))

Avanafil was generally well tolerated. In total, 37.9% (183/483) of men who received

avanafil treatment and 26.1% (42/161) of men who received placebo experienced an adverse event (statistical analysis not reported). The most frequently reported adverse events, occurring in more than 2% of men in any treatment group, included headache, flushing, nasal congestion, back pain, nasopharyngitis and bronchitis. No treatment-related serious adverse events were seen.

A total of 96 (14.9%) men discontinued the study, primarily due to lack of compliance with the protocol (8.2%) or loss to follow-up (3.4%). In the placebo, avanafil 50 mg, 100 mg and 200 mg groups respectively, 5, 3, 6 and 2 men discontinued treatment due to adverse events (statistical analyses not reported).

Type 1 or type 2 diabetes mellitus ([Goldstein et al. 2012b](#))

Avanafil was generally well tolerated. Overall, 33.3% (86/258) of men who received avanafil and 23.8% (31/130) men who received placebo reported 1 or more adverse event (statistical analysis not reported). Events that occurred in at least 2% of men in any treatment group included headache, nasopharyngitis, flushing, sinus congestion, back pain, sinusitis, dyspepsia, and influenza. All drug-related adverse events were reported to be mild to moderate in severity. None of the serious adverse events reported were considered treatment-related.

Of the 57 (14.6%) men who discontinued the study, 4 (0.1%; 2 taking avanafil 100 mg and 2 taking avanafil 200 mg) discontinued because of adverse events, 36 (9.2%) discontinued because of protocol noncompliance, and 15 (3.8%) were lost to follow-up.

Bilateral nerve-sparing radical prostatectomy ([Mulhall et al. 2013](#))

Avanafil was generally well tolerated. Adverse events were reported in 41.9% (83/198) of men who received avanafil and 23.0% (23/100) men who received placebo (statistical analysis not reported). The most frequently reported adverse events were headache, flushing and nasopharyngitis. No serious adverse events were reported during the study.

Overall, 46 (15.4%) men discontinued the study, primarily due to withdrawal of consent (23 [7.7%]) and loss to follow-up (10 [3.4%]). Five (1.7%) men discontinued due to an adverse event (1 in the placebo group, 2 in the avanafil 100 mg group and 2 in the avanafil 200 mg group).

Open-label long-term extension study ([Belkoff et al. 2013](#))

Avanafil was generally well tolerated. In this 52-week study (mean treatment duration 35.3 weeks), 38.7% (275/711) of men reported adverse events. In 11.1% of men, these were considered to be drug-related. None of the serious adverse events reported were considered treatment-related. The most frequently reported adverse events, seen in at least 2% of men, were headache, flushing and nasopharyngitis and nasal congestion.

The overall discontinuation rate was 30.6% (220/712) and discontinuations due to adverse events occurred in 2.8% (20/712) of men. Other key reasons for discontinuation were loss to follow-up, protocol noncompliance, and withdrawal of consent. The percentage of men who discontinued the study was lower among those who received avanafil 100 mg and 200 mg (25.9%) than among those who received avanafil 100 mg only (46.2%; statistical analysis not reported). Discontinuations due to adverse events were also lower among men who received both doses (1.5%) than among those who received avanafil 100 mg only (6.4%; statistical analysis not reported).

Summary of product characteristics (Spedra)

The summary of product characteristics states that the most common adverse events reported in clinical studies (n=2144) were headache, flushing, nasal and sinus congestion (all with an incidence of between 1 in 10 and 1 in 100), and back pain (incidence between 1 in 100 and 1 in 1000). Overall, adverse events were more frequent in men with a normal body mass index (BMI; less than 25 kg/m²). In the long-term clinical study, the percentage of men who experienced adverse events decreased with increasing length of exposure.

Men should be aware of how they react to avanafil before driving or using machines because dizziness, somnolence and altered vision were reported in clinical studies with avanafil (incidence between 1 in 100 and 1 in 1000).

Evidence strengths and limitations

The 3 double-blind RCTs evaluating the safety and efficacy of avanafil in men with erectile dysfunction in the general population (Goldstein et al. 2012a), with diabetes mellitus (Goldstein et al. 2012b), and post-prostatectomy (Mulhall et al. 2013) were generally well designed. However, all of the studies are placebo-controlled and it is not known how avanafil compares to other PDE5 inhibitors. In addition, some data for the primary outcomes are missing in Mulhall et al. (2013) and no confidence intervals are provided for the data in any of the RCTs.

No p values or confidence intervals are reported in the long-term extension study ([Belkoff et al. 2013](#)). Other limitations of this study include the lack of a comparator and blinding, and the possibility that men who experienced a response to avanafil in the qualifying studies may have been more likely to enrol than men who did not, potentially overestimating the benefits of avanafil. Dropout rates were around 15% in the 3 RCTs and 30% in the long-term extension study. However, analyses were by intention-to-treat and few discontinuations were due to adverse events.

The majority of men included in the 4 studies were white (80–86%), which limits the generalisability of the results to other races. Also, the average age of participants was about 56–58 years: limited data are available in older men aged 70 years or above (see the summary of product characteristics). Men with mild, moderate and severe erectile function domain scores were well represented in the studies undertaken in the general and diabetic populations: 71.5% of men in the post-prostatectomy study ([Mulhall et al. 2013](#)) had severe erectile dysfunction.

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, avanafil 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. Only 10.5% of participants in [Goldstein et al. \(2012b\)](#) had type 1 diabetes, which limits the study's applicability to men with this condition.

In the European public assessment report for avanafil, the CHMP notes that the average weight, height and BMI of participants in the studies, which were carried out in the US, are not generalisable to many regions in Europe. An increased frequency of adverse events was seen in men with a normal BMI (18.5–25kg/m²) compared with overweight and/or obese men.

In the RCTs, about three-quarters of men had previously used PDE5 inhibitors. However, it is not known whether avanafil is effective in men whose erectile dysfunction has consistently failed to respond to other PDE5 inhibitors, or whether it is tolerated by men who have experienced dose-limiting adverse effects with another of these drugs, because these populations were excluded from the studies. The CHMP questioned whether the study population was an enriched population, favouring the observed efficacy results, but the company argued that by defining treatment failure as 'the failure to respond to 2 or more specific PDE5 inhibitors, with each used on multiple attempts', the company tried to identify men unresponsive to PDE5 inhibitor therapy as a class, rather than to a single

agent ([European public assessment report for avanafil, 2013](#)).

During their assessment of avanafil, the CHMP questioned the lack of a pre-planned definition of 'responders' and '[clinically significant](#)' change from baseline for the 3 co-primary endpoints. In response to this, a post-hoc analysis was provided, which defined the minimum thresholds for clinically relevant changes from baseline for successful intercourse, vaginal penetration and IIEF as improvements of 23%, 21% and more than 4 points respectively ([European public assessment report for avanafil, 2013](#)).

All studies were funded by the companies involved in the development of avanafil, [Vivus](#) and [Mitsubishi Tanabe Pharma Corporation](#). ([Menarini](#) has been granted the rights to market avanafil in Europe).

Context

Alternative treatments

First-line therapy for erectile dysfunction is usually an oral selective phosphodiesterase type 5 (PDE5) inhibitor. Alternatives to avanafil are sildenafil, tadalafil and vardenafil. All are used as required: tadalafil can also be used daily at lower doses. The choice of PDE5 inhibitor depends on the frequency of intercourse (occasional or 3–4 times weekly) and the man's personal experience of these drugs ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)), as well as efficacy, safety and cost.

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 only be prescribed on the NHS under certain circumstances (see individual preparations in the [British National Formulary](#)).

Other treatment options include vacuum erection devices, and intracavernous, intraurethral and topical alprostadil. Surgical implantation of a penile prosthesis may be considered in men who fail pharmacotherapy or who want a permanent solution ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)).

Costs of alternative treatments

Table 3 Costs of PDE5 inhibitors

	Dose	Directions for use ^a	Estimated cost (excluding VAT)
Avanafil tablets	50 mg	Usual starting dose 100 mg as needed 30 minutes before sexual activity. Maximum 1 daily	£10.94 for 4 ^b £19.70 for 8 ^b
	100 mg		£14.08 for 4 ^b £26.26 for 8 ^b
	200 mg		£21.90 for 4 ^b £39.40 for 8 ^b
Sildenafil tablets	25 mg	Usual starting dose 50 mg as needed 1 hour before sexual activity. Maximum 1 daily	£1.23 for 4 ^c
	50 mg		£1.08 for 4 ^c
	100 mg		£1.15 for 4 ^c
Tadalafil tablets	2.5 mg	1 daily	£54.99 for 28 ^c
	5 mg	1 daily	£54.99 for 28 ^c
	10 mg	Usual starting dose 10 mg as needed 30 minutes before sexual activity. Maximum 1 daily	£26.99 for 4 ^c
	20 mg		£26.99 for 4 ^c
Vardenafil orodispersible tablets	10 mg	1 as needed 25–60 minutes before sexual activity. Maximum 1 daily	£17.88 for 4 ^c
^a Doses taken from the summaries of product characteristics ^b Costs taken from MIMS , June 2014 ^c Costs taken from Drug Tariff , June 2014			

Estimated impact for the NHS

Likely place in therapy

Avanafil statistically significantly improved the percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse; the

percentage of sexual attempts in which vaginal penetration was achieved; and [International Index of Erectile Function](#) erectile function domain scores compared with placebo. The majority of improvements were of [clinical importance](#) and avanafil was well tolerated. However, it is not known how the efficacy and safety of avanafil compare with the other PDE5 inhibitors, sildenafil, tadalafil and vardenafil. There are no direct head-to-head comparisons and indirect comparisons are limited by differences between the studies (for example, study designs, populations, outcomes, rating scales and definitions of success).

According to the [European Association of Urology guidelines on male sexual dysfunction](#), sildenafil is effective 30–60 minutes after administration and efficacy may be maintained for up to 12 hours. Efficacy rates (erection rigidity sufficient for vaginal penetration) are 56%, 77% and 84% in men taking 25 mg, 50 mg and 100 mg of sildenafil, respectively. The efficacy of sildenafil has been well established in most subgroups of men with erectile dysfunction and there is more cumulative experience with sildenafil than with the other PDE5 inhibitors ([NICE Clinical knowledge summary: erectile dysfunction](#)).

Tadalafil is effective from 30 minutes after administration but its peak efficacy occurs after about 2 hours and efficacy is maintained for up to 36 hours. Efficacy rates are 67% and 81% in men taking 10 mg and 20 mg of tadalafil, respectively. Although PDE5 inhibitors were introduced as on-demand treatment, tadalafil has also been approved for continuous, everyday use at 2.5 mg and 5 mg doses ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)).

Vardenafil is effective 30 minutes after administration. Efficacy rates are 66%, 76% and 80% in men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively ([European Association of Urology guidelines on male sexual dysfunction, 2014](#)).

A [systematic review and meta-analysis](#) (Yuan J et al. 2013: 118 RCTs, n=31,195) has compared the efficacy and safety of PDE5 inhibitors for erectile dysfunction. It found that, compared with sildenafil, tadalafil and vardenafil, avanafil was statistically significantly less effective on [Global Assessment Questionnaire question 1](#) ('Has the treatment you are taking improved your erectile function?') and there were no major differences in safety between PDE5 inhibitors. However, the systematic review included only 2 RCTs of avanafil ([Goldstein et al. 2012a](#) and [Zhao et al. 2012](#)) and inadequate data were available to include avanafil in the meta-analysis for any other outcomes. Therefore, limited information is available about the relative efficacy and safety of avanafil.

It is also not possible to draw conclusions around the efficacy and tolerability of avanafil in men whose erectile dysfunction has consistently not responded to other PDE5 inhibitors, or whether it is tolerated by men who have experienced dose-limiting adverse effects with another of these drugs, because these men were excluded from studies.

The [European guidelines on male sexual dysfunction](#) advise that the choice of PDE5 inhibitor depends on the frequency of intercourse (occasional or 3–4 times weekly) and the man's personal experience of these drugs. Onset of action might be important to some men taking PDE5 inhibitors on-demand. According to the [summaries of product characteristics](#), sildenafil should be taken 1 hour before sexual activity, whereas avanafil, tadalafil (10 mg and 20 mg) and vardenafil should be taken 25–30 minutes before sexual activity.

Although the [summary of product characteristics](#) currently states that avanafil should be taken approximately 30 minutes before sexual activity, the manufacturer, Menarini, has advised that a licence variation to examine the therapeutic effect of avanafil approximately 15 minutes after dosing in men with mild to severe erectile dysfunction has been submitted to the [European Medicines Agency](#) and a decision is expected later in 2014 (Menarini; personal communication, June 2014).

According to a secondary analysis in [Goldstein et al. \(2012a\)](#), 300 sexual attempts were made within 15 minutes of dosing and, of these, 64–71% attempts were reported to be successful in the avanafil groups compared with 27% in the placebo group. However, the [European public assessment report for avanafil](#) states that the time from drug intake to the start of the sexual activity was not well defined during the studies. Based on the men's diary responses, the percentages of success at different time periods are very similar (from earliest times up to 4–6 hours post-dose), which precluded the Committee for Medicinal Products for Human Use from reaching any definitive conclusions about the onset of action. If the license extension is approved, any new evidence on a 15 minute effectiveness window will need to be assessed before any recommendations can be made in this regard.

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 avanafil for erectile dysfunction. When usual starting doses are considered, avanafil costs significantly more than generic sildenafil (£14.08 for 4 x 100 mg tablets compared with £1.08 for 4 x 50 mg tablets) but is competitively priced compared with on-demand tadalafil (£26.99 for 4 x 10 mg tablets) and vardenafil (£17.88 for 4 x 10 mg tablets).

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 only be prescribed on the NHS under certain circumstances (see individual preparations in the [British National Formulary](#)).

Estimated usage

A Department of Health [impact assessment](#) for the [proposed changes to the NHS availability of treatment for erectile dysfunction](#) estimated that the total prevalence of drug therapy for erectile dysfunction is about 184,000 and the number of men being prescribed a PDE5 inhibitor within UK primary care at any one time is about 177,000. This figure is likely to increase if prescribing restrictions are removed.

It has been suggested that about 40% of men discontinue their first-line PDE5 inhibitor therapy because of lack of efficacy ([Carvalho et al. 2012](#)). Assuming that there are 177,000 men receiving treatment at any one time, this suggests that an estimated 70,800 men might be considered for a second-line alternative. Assuming a market penetration for avanafil that is the same as the third to market (vardenafil, 7.7%), about 5000 men might be prescribed avanafil second-line in the UK at any one time. This is around 3% of the 177,000 men receiving treatment with a PDE5 inhibitor. The manufacturer notes that this is an appropriate market share for a fourth to market drug (Menarini; personal communication, March 2014). However, specialists involved in the production of this evidence summary have advised that it might be an overestimation, primarily due to the increasing impact of generic sildenafil.

Relevance to NICE guidance programmes

Avanafil was not considered appropriate for a NICE technology appraisal and is not currently planned into any other 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 clinical guideline 8) advises that men with multiple sclerosis should be asked whether they experience erectile dysfunction and, if so, whether it is of concern. Sildenafil 25–100 mg should be offered to men who have persisting erectile dysfunction unless it is contraindicated. [An update of this guideline is in progress.](#)

- [Diagnosis and management of type 1 diabetes in children, young people and adults](#) (NICE clinical guideline 15) advises that men should be asked annually whether erectile dysfunction is an issue and a phosphodiesterase-5 (PDE5) inhibitor, if not contraindicated, should be offered where erectile dysfunction is a problem.
- [Type 2 diabetes - newer agents \(partial update of CG66\)](#) (NICE clinical guideline 87) advises that the issue of erectile dysfunction should be raised annually in men with type 2 diabetes. Assessment and education for men with erectile dysfunction should be provided to address contributory factors and treatment options and a PDE5 inhibitor should be offered (choosing the drug with the lowest acquisition cost), in the absence of contraindications, if erectile dysfunction is a problem. [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 clinical guideline 172) 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 clinical guideline 175) states that men with prostate cancer should have early and ongoing access to specialist erectile dysfunction services.

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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

No relevant interests declared.

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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