

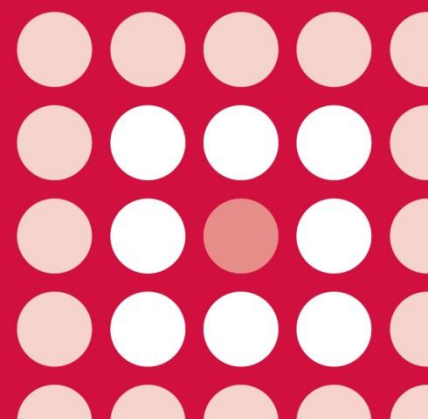


AWMSG SECRETARIAT ASSESSMENT REPORT

Avanafil (Spedra[®]▼)
50 mg, 100 mg and 200 mg tablets

Reference number: 1261

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report Avanafil (Spedra[®]▼) 50 mg, 100 mg and 200 mg tablets

This assessment report is based on evidence submitted by A. Menarini Farmaceutica Internazionale SRL on 09 February 2015¹.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Avanafil (Spedra [®] ▼) for the treatment of erectile dysfunction in adult men ² .
Dosing	The recommended dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment. Refer to the Summary of Product Characteristics (SPC) for further dosing information ² .
Marketing authorisation date	21 June 2013 ³ .

2.0 DECISION CONTEXT

2.1 Background

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance^{4,5}. Erectile dysfunction affects both physical and psychosocial health and has a significant impact on the quality of life of sufferers and their partners⁵⁻⁷. Approximately 52% of men aged 40–70 years have some degree of erectile dysfunction (minimal to complete), with prevalence and severity increasing with age⁵⁻⁷. It is estimated that 177,000 men are currently treated with phosphodiesterase type 5 (PDE5) inhibitors in England and Wales⁸. 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 medicines (such as antihypertensive treatments)^{4,6,7}.

European Guidelines recommend first-line treatment with selective PDE5 inhibitors such as sildenafil, vardenafil and tadalafil⁵. Avanafil is a highly selective and potent inhibitor of PDE5^{2,6,9}. When sexual stimulation causes the local release of nitric oxide, avanafil inhibits PDE5 resulting in smooth muscle relaxation and an influx of blood flow into the penile tissues, thereby producing an erection. Avanafil's pharmacokinetic profile results in an onset of action of 15–30 minutes. Avanafil has no effect in the absence of sexual stimulation^{2,6,9}.

The applicant company has suggested that avanafil should be considered for the second-line treatment of erectile dysfunction in men who are not satisfied, intolerant or unresponsive to first-line treatment with generic sildenafil¹.

2.2 Comparators

The comparators included in the company submission were:

- Sildenafil (Viagra[®])
- Vardenafil (Levitra[®])
- Tadalafil (Cialis[®])

2.3 Guidance and related advice

- European Association of Urology. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation (2014)⁵.
- All Wales Medicines Strategy Group (AWMSG). All Wales guidance on prescribing for erectile dysfunction (2012)¹⁰.
- British Society for Sexual Medicine (BSSM). Guidelines on the management of erectile dysfunction (2009)⁴.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details from three pivotal randomised controlled trials (RCTs) which described the efficacy and safety of avanafil for the treatment of erectile dysfunction in adult men (studies TA-301, TA-302 and TA-303) versus placebo¹. The submission also included an open-label extension study (TA-314) and a phase IV double-blind trial (TA-501); these will not be discussed further¹. In the absence of head-to-head evidence for the efficacy and safety of avanafil versus the other available PDE5 inhibitors, the applicant company also provided indirect and mixed treatment comparisons^{1,11,12}.

3.1 Pivotal studies (TA-301, TA-302 and TA-303)

Three RCTs (total n = 1,334) have evaluated the use of avanafil in adult men for the treatment of erectile dysfunction, in the general population (TA-301)¹³; in patients with diabetes mellitus (TA-302)¹⁴; and following prostatectomy (TA-303)¹⁵. Overall, when compared with placebo, avanafil 50 mg, 100 mg and 200 mg elicited a statistically significant improvement in all three co-primary endpoints, including Sexual Encounter Profile question 2 (SEP2; the percentage of sexual attempts in which vaginal penetration was achieved) and question 3 (SEP3; the percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse); and changes to the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score (see Glossary)^{1,6,9,13–15}. Higher response rates were observed with avanafil in the general population with erectile dysfunction, than in those with diabetes or prostatectomy. Response rates generally decreased as the severity of erectile dysfunction increased^{6,9}.

3.2 Meta-analyses by Yuan et al (2013) and Wang et al (2014)

Yuan et al (2013) performed a systematic literature review and network meta-analysis of PDE5 inhibitors versus placebo as treatments for erectile dysfunction¹². Of the 118 studies included, there were two avanafil trials, one of which was TA-301. Using the self-administered Global Assessment Questionnaire, avanafil was reported as less effective based on question 1 (while using the study medication, did you feel that your erections improved?) as compared to tadalafil (relative risk [RR]: 0.61; 95% confidence interval [CI]: 0.33–0.9) and vardenafil (RR: 0.63; 95% CI: 0.35–0.92). For all efficacy outcomes, the absolute effects and rank tests indicated that tadalafil and vardenafil were the most effective agents¹². Wang et al (2014) published a systematic review and meta-analysis to compare the effectiveness and safety among different dosages of avanafil for the treatment of erectile dysfunction, comparing against placebo¹¹. Results from Yuan et al (2013) and Wang et al (2014) are presented as part of Table 1.

3.2.1 Mixed treatment comparison (Yuan et al [2013] versus Wang et al [2014])

The applicant company indirectly compared the two meta-analyses described in Section 3.2 (Yuan et al [2013] and Wang et al [2014]), and results are provided in Table 1^{1,11,12}.

Table 1. Overview of outcomes reported in meta-analyses (Yuan et al [2013] versus Wang et al [2014])¹

	SEP3, mean difference from baseline (95% CI)	SEP2, mean difference from baseline (95% CI)	IIEF-EF domain score, mean difference from baseline (95% CI)
Sildenafil	17.3 (5.9–28.6)	8.7 (1.9–15.5)	6.0 (5.3–6.7)
Tadalafil	36.2 (31.9–39.9)	27.7 (24.1–31.4)	7.5 (6.6–8.3)
Vardenafil	36.3 (4.0–41.3)	27.4 (23.3–31.5)	7.1 (6.0–8.2)
Avanafil	22.8 (16.5–28.9)	20.7 (15.2–25.9)	5.2 (3.9–6.5)

CI: confidence interval; IIEF-EF: International Index of Erectile Function-Erectile Function; SEP3: percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse; SEP2: percentage of sexual attempts in which vaginal penetration was achieved

3.2.2 Mixed treatment comparison (based on Yuan et al [2013])

The applicant company conducted a systematic literature review and mixed treatment comparison utilising Bayesian network meta-analysis to compare the efficacy of avanafil with tadalafil and with vardenafil¹. The applicant company applied additional selection criteria to the studies identified in the systematic review conducted by Yuan et al (2013), including: SEP3 as a primary endpoint; a fixed-dose treatment arm; recommended initiation doses and 12-week primary endpoints. Studies that included patients with a single aetiology were excluded. Of the 118 studies identified by Yuan et al (2013), 11 met the applicant company's selection criteria¹. A further eight studies were identified and were included in a sensitivity analysis of 4-week data¹. To minimise the influence of expected study heterogeneity, the mixed treatment comparisons were performed using two random effects models.

The Bayesian network meta-analysis found no credible evidence for a difference in efficacy between avanafil and tadalafil or vardenafil as measured by SEP3¹.

3.3 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that the adverse event (AE) profile of avanafil is concordant with those known for other PDE5 inhibitors already authorised and that no new safety concerns have been observed with avanafil⁹. As with other PDE5 inhibitors, AEs caused by avanafil were generally mild to moderate in severity^{9,11,12}. The most common AEs reported were flushing and headache⁹. Avanafil, 50–200 mg is well tolerated for the treatment of erectile dysfunction, and an increase in dosage is not associated with a significant increase in AEs^{9,11}.

3.4 AW TTC critique

- Avanafil was statistically significantly more effective than placebo, but there are no head-to-head comparisons with sildenafil, tadalafil and vardenafil. The network meta-analysis mixed treatment comparison of the PDE5 inhibitors are limited by differences in the studies (population, outcomes, doses, rating scales, definitions of success).
- The applicant company suggest that avanafil should be considered for second-line use following treatment failure with generic sildenafil¹; however men whose erectile dysfunction had consistently not responded to other PDE5 inhibitors, or men who had experienced dose-limiting AEs with other PDE5 inhibitors were excluded from the pivotal studies.
- The average age in the avanafil studies was 56-58 years⁶ and there was limited data for men aged 70 years and older^{6,9}. It is unclear whether the efficacy and safety profiles have been well characterised in this subgroup of elderly patients⁹.
- The criteria for inclusion of trials in the network meta-analysis exclude data that are relevant to the proposed use of avanafil and the comparators in NHS Wales, e.g. data from trials conducted specifically in patients with diabetes mellitus who meet the current eligibility criteria for the prescribing of PDE5 inhibitors on the NHS.
- Avanafil has a quicker onset of action than other PDE5 inhibitors and can be taken 15–30 minutes prior to sexual activity, compared to 30 minutes, 25–60 minutes and 60 minutes for tadalafil, vardenafil and sildenafil, respectively^{2,16–18}. The company suggest that this may be an advantage in terms of spontaneity and immediacy for sexual activity¹.
- Avanafil is currently available only as an oral tablet formulation for ‘on demand’ dosing². Other PDE5 inhibitors are available as orodispersible formulations¹⁹, and tadalafil is also licensed for once daily dosing in those anticipated to engage in intercourse more than twice per week¹⁷.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost minimisation analysis (CMA) of avanafil at ‘on-demand’ doses of 100 mg or 200 mg as a second-line treatment for erectile dysfunction following first-line treatment with generic sildenafil¹. As the licensed indication for avanafil does not limit its use to second-line treatment, the company has effectively restricted its economic evidence to a subset of the licensed population. The comparators are tadalafil 10 mg and 20 mg, vardenafil 10 mg and 20 mg, and branded sildenafil (Viagra[®]) 50 mg and 100 mg tablets; a comparison of avanafil 50 mg with vardenafil 5 mg has not been considered¹.

The CMA framework assumes therapeutic equivalence in all domains of health outcomes; however, there are no direct comparative trial data for avanafil and the comparators. To support the assumption of equivalence, the company has conducted a Bayesian network meta-analysis of trials of tadalafil, vardenafil, and avanafil. Included studies were limited to fixed-dose trials reporting responses to SEP3. All trials of sildenafil, any trials of orodispersible formulations, and trials that exclusively recruited patients with single erectile dysfunction aetiologies (i.e. trials conducted exclusively in patients with erectile dysfunction due to diabetes mellitus, or erectile dysfunction due to prostatectomy), were excluded from the meta-analysis. The results are reported to show that tadalafil 10 mg, vardenafil 10 mg and avanafil 100 mg are all significantly more effective than placebo, and there are no statistically significant differences between these agents at these doses when efficacy is measured by SEP3¹.

The CMA is conducted using Prescription Cost Analysis data for Wales from July 2014 to determine current use of the comparators, from which the costs had avanafil been used instead are estimated using current British National Formulary (BNF) list prices²⁰. A one year time horizon is considered¹.

4.1.2 Results

The company's estimates of annual per patient cost savings and total annual cost savings to NHS Wales, assuming avanafil replaces all comparators and constant prescribing rates, are presented in Table 2. Avanafil is estimated to be cost saving by around 27% per patient treated, which is estimated to save NHS Wales £817,366 per year compared with use of the existing comparators combined.

Table 2. Results of base case CMA

Treatment	Cost per year
Avanafil (simulated average dosing and quantities prescribed)	£298.52 per patient
Tadalafil, vardenafil and Viagra [®] combined (weighted average dosing and quantities prescribed)	£408.03 per patient
Cost savings to NHS Wales, based on estimated 7,464 prescription items per month	£817,366

No sensitivity or scenario analyses have been conducted.

4.1.3 AW TTC critique

The economic evidence provided by the company is limited to use of avanafil at 'on-demand' dosing of 100 mg or 200 mg as a second-line treatment for erectile dysfunction following first-line sildenafil.

As there are no direct comparative trials of avanafil and the comparators, network meta-analyses have been conducted. Based on these, avanafil is estimated to have comparable efficacy to tadalafil and vardenafil. However, there are limitations to these analyses. Details of the literature searches used to identify relevant trials are limited. The majority of patients enrolled in the included trials were known responders to PDE5 inhibitors, with few reported to have experienced failure. The extent to which these trials would reflect equivalence in the company's proposed NHS use of avanafil as a second-line agent following first-line use of sildenafil is unclear. The cost estimates, and hence cost savings, are influenced by the assumed proportions of patients taking the avanafil 100 mg or 200 mg doses, and the assumed comparator dose equivalents (10 mg and 20 mg, respectively). However, under an assumption of therapeutic equivalence, avanafil is less costly or cost neutral compared with available branded alternatives based on current NHS list prices.

Key strengths of the economic evidence include:

- In the absence of direct comparative trial data for avanafil and the comparators, the company has conducted network meta-analyses/adjusted, indirect comparisons of trial data in an attempt to strengthen the assumptions of therapeutic equivalence.

Key limitations and uncertainties of the economic evidence include:

- There are no direct comparative data for avanafil and the comparators. To indirectly compare these agents, network meta-analyses have therefore been necessary, which are associated with some limitations as outlined above.
- The CMA framework assumes therapeutic equivalence in all domains of health outcomes; however, demonstration of equivalence of avanafil and the comparators is limited:

- The company's network meta-analyses consider one key efficacy measure achieved with avanafil 100 mg compared with tadalafil 10 mg and vardenafil 10 mg to support the assumption of therapeutic equivalence. Comparisons of other efficacy and safety endpoints were not conducted, and comparisons of other licensed doses are not provided.
- The CMA provided by the company is therefore limited to 'on-demand' dosing of avanafil and comparators, in patients who do not require the lower doses specified in the respective Summaries of Product Characteristics (SPCs)^{2,16–18}.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTTC have not identified any published evidence on the cost-effectiveness of avanafil of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Prescription Cost Analysis data from July 2014, and assuming one prescription item per patient per month, the company estimates there are around 21,405 patients treated with PDE5 inhibitors in Wales. Of these, around 7,500 are estimated to receive tadalafil, vardenafil and the Viagra[®] branded version of sildenafil¹. The incidence of new prescriptions for generic sildenafil has risen at a linear rate between January 2013 and July 2014, representing a growth of approximately 4,100 new cases per year. As the prescribing of generic sildenafil was, until September 2014, restricted to patients with conditions listed under Part XVIII B of the Drug Tariff (Drugs, Medicines and Other Substances that may be ordered only in certain circumstances), and these restrictions apply equally to avanafil and its comparators, the company assumes that the incident cases predicted from generic sildenafil prescribing will be eligible for treatment with proprietary PDE5 inhibitors where necessary. Uptake of avanafil is therefore estimated to occur among these incident cases, along with switching from existing use of tadalafil and vardenafil on cost grounds.

Based on estimates in the literature of discontinuations of PDE5 inhibitors due to lack of efficacy²¹, the company estimates 18% of the 4,100 incident cases would be eligible for second-line treatment, of which 51% would continue on treatment in subsequent years. Of the existing cases treated with tadalafil and vardenafil (10 mg and 20 mg), it is expected that 30% of patients will be switched to avanafil on cost grounds, but thereafter the increasing proximity of generic alternatives would reduce incremental switching to +15% in year two, and +7.5% in year three. No discontinuations among these patients is assumed.

5.1.2 Results

The company has provided cumulative budget impact estimates for the first three years only, on the basis of greater uncertainty associated with estimates beyond that period due to the patent expiry for tadalafil and vardenafil, and subsequent introduction of generic alternatives.

Table 3. Company budget impact estimates

	Year 1 (2015/16)	Year 2 (2016/17)	Year 3 (2017/18)
Number of potentially eligible patients: second-line PDE5 inhibitors.	773	1,167	1,562
Current users of tadalafil and vardenafil	7,307	7,307	7,307
Uptake – second-line PDE5 inhibitors (%)	40%	70%	90%
Uptake – switchers from tadalafil and vardenafil (cumulative %)	30%	45%	53%
Number of avanafil treated patients	2,965	4,456	5,398
Overall net cost (cumulative)	–£226,172	–£598,371	–£1,076,719

In an alternative uptake scenario, if switching amongst prevalent cases were to increase (on price advantage) to 50% in year one, +25% in year two, and +12% in year three, the cumulative saving to NHS Wales would be –£366,883 in year one, –£950,150 in year two and –£1,674,744 in year three¹.






5.1.3 AWTTTC critique


- The company has adopted a pragmatic approach to estimate potentially eligible patient numbers. Welsh prescribing data for comparators have been used to estimate the number of patients with erectile dysfunction potentially eligible for avanafil, assuming one prescription item per month equates to one patient.
- Uptake estimates are a source of uncertainty as in all budget impact estimates.
- The analysis relates only to the use of avanafil 100 mg or 200 mg, and tadalafil and vardenafil 10 mg and 20 mg 'on-demand' doses.
- Collectively, the likely budget impact of use of avanafil is subject to uncertainty; however, under the assumption of therapeutic equivalence, irrespective of the number of patients treated, use of avanafil (100 mg and 200 mg) would be less costly than use of tadalafil (10 mg and 20 mg) and less costly or cost neutral with vardenafil (10 mg and 20 mg) at current list prices; however vardenafil 5 mg is less costly than avanafil 50 mg.

5.2 Comparative unit costs

Example comparative costs of avanafil and alternative PDE5 inhibitors are presented in Table 4.

Table 4. Example annual costs of avanafil and comparators for the treatment of erectile dysfunction

Medicine	'on-demand' dose	Cost per 4-pack	Cost per 8-pack*
Avanafil (Spedra [®] ▼)  tablet	50 mg	£10.94	£19.70
	100 mg	£14.08	£26.26
	200 mg	£21.90	£39.40
Sildenafil (non-proprietary) tablet	25 mg	£1.12	£2.09
	50 mg	£1.16	£2.23
	100 mg	£1.25	£2.32
Sildenafil (Viagra [®])  tablet	25 mg	£16.59	£33.19
	50 mg	£21.27	£42.54
	100 mg	£23.50	£46.99
Tadalafil (Cialis [®])  tablet	2.5 mg*	£54.99 for 28-pack	
	5 mg*	£54.99 for 28-pack	
	10 mg	£26.99	–
	20 mg	£26.99	£53.98
Vardenafil (Levitra [®])  tablet	5 mg	£7.56	£15.12
	10 mg	£14.08	£28.16
	20 mg	£23.48	£46.96
Vardenafil (Levitra [®])  orodispersible	10 mg	£17.98	–

This table does not imply therapeutic equivalence of medicines or doses.
* Based on BNF list price²⁰. Tadalafil 2.5 mg and 5 mg dose licensed for once daily use with price based on 28-day pack.
See relevant Summaries of Product Characteristics (SPCs) for full dosing details^{2,16–19}.
 Not prescribable on the NHS for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XI B of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed 'SLS'.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, avanafil (Spedra[®]▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that avanafil (Spedra[®]▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted that evidence from study TA-501 is likely to be available within 6–12 months¹.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 23 February 2015

Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

International Index of Erectile Function- Erectile Function (IIEF-EF) domain score

The IIEF is a validated, self-administered, 15-item (five-domain) instrument designed to assess erectile function (mild = EF domain score of 17-25; moderate = EF domain score of 11-16; severe = EF domain score \leq 10). Studies included in the company submission assessed the change in IIEF-EF domain score from baseline to the end of the 12-week treatment period²².

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