Abbreviated New Medicine Assessment

Avanafil tablets (Spedra®)

For the treatment of erectile dysfunction in adult men

Recommendation: Green (Restricted)

Avanafil is recommended for the treatment of erectile dysfunction in adult men who are unable to tolerate sildenafil and tadalafil.

Background and context

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. It is a symptom and not a disease and may be due to multiple underlying causes. Erectile dysfunction is caused by various vascular, neuronal, hormonal, and metabolic factors, mediated by endothelial and smooth muscle dysfunction, as normal erectile function relies on arterial dilatation, smooth muscle relaxation, and veno-occlusion within the penile corpora.

Erectile dysfunction is a very common disorder, and the incidence and prevalence increases with age (crude incidence rate of 25.9 per 1000 man-years). Depending on the likely underlying cause of erectile dysfunction (obesity, CVD, diabetes, neurogenic, psychogenic, drug-induced etc) some cases can be cured, and others may be managed successfully with medical or surgical treatment. For men not at high cardiac risk of sexual activity, the NICE CKS recommends considering prescribing drug treatment with a phosphodiesterase-5 (PDE-5) inhibitor, irrespective of the suspected underlying cause(s). Drug choice depends on the frequency of intercourse, speed of onset, duration of action, dosing regimen, personal experience and preference, adverse effect profile, cost, and local prescribing guidelines. Avanafil is listed as an option alongside sildenafil, tadalafil and vardenafil. [1]

Avanafil for erectile dysfunction was prioritised for review following a request from Fylde Coast sub ICB location.

Summary of evidence

Summary of efficacy data in proposed use:

Meta-analysis of avanafil RCTs [2]

This study reviewed and meta-analysed the RCTs on the effect of avanafil in patients with erectile dysfunction. The study included 5 RCTs including 1,379 and 605 patients in active and placebo groups. The authors concluded that avanafil was up to 3-fold superior to placebo in determining successful sexual intercourse and that avanafil had comparable efficacy, but lower incidence of drug-related side effects, compared to first-generation PDE5is.

Network Meta-analysis of oral phosphodiesterase 5 inhibitors [3]

Date: June 2023

A systematic review with network meta-analysis compared oral-phosphodiesterase 5 inhibitors (PDE-5i). The review included 179 randomised controlled trials of approximately 50,000 patients. All PDE5i were significantly more efficient than placebo. Sildenafil 25 mg was statistically superior to all interventions in enhancing the International Index of Erectile Function (IIEF) (a multi-dimensional self-report for the evaluation of male sexual function), followed by sildenafil 50 mg. Taladafil 10 mg and 20 mg also presented good profiles. Avanafil was a less effective intervention.

RCT comparing avanafil with sildenafil in the treatment of erectile dysfunction [4]

This prospective, randomised, double-blind, two-arm, active-controlled, parallel, multicenter, non-inferiority clinical study was carried out in patients with erectile dysfunction for at least 3 months and IIEF– Erectile Function domain score of <26 at enrolment.

A total of 220 patients were randomised to receive either avanafil tablets 100 mg or sildenafil tablets 50 mg in 1:1 ratio. After 4 weeks of treatment, 40.0% of patients in the avanafil group and 45.6% of patients in the sildenafil group required dose escalation to a high dose (avanafil 200 mg/sildenafil 100 mg). The difference in the mean change of IIEF– Erectile Function score from baseline in the two groups increased from week 4 (1.1, CI95%; 0.2 to 2.5) to week 8 (1.4, CI95%; 0.1 to 2.7) and week 12 (2.1, CI95% 0.8 to 3.5), showing non-inferiority at week 4, and superiority at week 8 and week 12. Avanafil also showed a faster onset of action.

Summary of safety data:

Adverse effects for avanafil are generally mild in nature. The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines have summarised the common adverse events of the four PDE5i as follows [5]:

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%	None	< 2%	None
Back pain	None	6.5%	None	< 2%
Myalgia	None	5.7%	None	< 2%

The use of avanafil is contraindicated in:

- Patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.
- Patients with severe hepatic impairment (Child-Pugh C).
- Patients with severe renal impairment (creatinine clearance < 30 mL/min).
- Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
- Patients with known hereditary degenerative retinal disorders.

- Patients who are using potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin).

The SPC for avanafil (Spedra®) cautions regarding the use of PDE5i in patients with cardiac disease. The SPC also warns about the risks relating to priapism, visual problems and hearing loss. [6]

Strengths and limitations of the evidence:

Strengths

- A meta-analysis of RCTs in avanafil confirmed that avanafil had comparable efficacy but lower incidence of drug-related side effects, compared to first-generation PDE5is.
- A RCT comparing avanafil 100 mg with sildenafil 50 mg found avanafil was superior to sildenafil in improving the IIEF and a faster onset of action.
- Avanafil demonstrates lower frequency of adverse events compared to other PDE5is.
- The EAU suggests avanafil as ideal when used in erectile dysfunction while wishing to minimise adverse effects due to it being a highly selective PDE5i.
- The All Wales Medicines Strategy Group (AWMSG) recommends avanafil for the treatment of erectile dysfunction.

Limitations

- A network meta-analysis found that Avanafil was a less effective intervention than sildenafil, tadalafil and vardenafil.
- Avanafil is not recommended by the Scottish medicines Consortium (SMC).
- Avanafil is considerably more expensive than other oral PDE5is.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Avanafil provides an additional treatment option for patients who have not responded to or cannot tolerate other oral PDE5is.
Financial implications of the intervention:
Avanafil is not likely to be recommended in place of sildenafil or tadalafil due to the large cost difference. However, avanafil may be recommended as a third line agent following the use of sildenafil/ tadalafil in patients unable to tolerate these agents. Vardenafil is likely to occupy a similar position to avanafil in the treatment pathway. Currently there are 1,774 items of vardenafil prescribed in the Lancashire and South Cumbria ICB at an average cost of £11.86. If avanafil (costs range between £10.94 and £21.90) was used in vardenafil's place, the net impact on spend would be **-£1,600 to £17,810**. It is therefore expected that the use of avanafil will be cost neutral.
Service Impact Issues Identified:

No additional service impact would be anticipated due to the supply of avanafil as this is an additional treatment option.
Equality and Inclusion Issues Identified:
Include the summary of the outcome of the screening tool.
Cross Border Issues Identified:
GMMMG do not list avanafil in their RAG list. Pan Mersey have classified avanafil as a Green Medicine (Third Choice- alongside vardenafil).
Legal Issues Identified:
N/A
Media/ Public Interest:
The ICB has previously received a complaint from a patient relating to the decision to assign avanafil a “Do not Prescribe” RAG status.

References

[1] NICE, "Clinical Knowledge Summary: Erectile Dysfunction," May 2023. [Online]. Available: https://cks.nice.org.uk/topics/erectile-dysfunction/. [Accessed June 2023].

[2] G Corona et al, "The safety and efficacy of Avanafil, a new 2nd generation PDE5i: comprehensive review and meta-analysis," *Expert Opinion on Drug safety,* vol. 15, no. 2, pp. 237-247, 2016.

[3] CR Madeira et al, "Efficacy and safety of oral phosphodiesterase 5 inhibitors for erectile dysfunction: a network meta-analysis and multicriteria decision analysis," *World Journal of Urology,* vol. 39, pp. 953-96, 2021.

[4] M Kumar et al, "Efficacy and safety of avanafil as compared with sildenafil in the treatment of erectile dysfunction: A randomized, double blind, multicenter clinical trial," *International Journal of Urology,* vol. 29, pp. 351-359, 2022.

[5] The European Association of Urology, "Sexual and Reproductive Health Guidelines," 2023. [Online]. Available: https://uroweb.org/guidelines/sexual-and-reproductive-health. [Accessed 28 June 2023].

[6] Electronic Medicines Compendium, "Summary of Products Characteristics," A. Menarini Farmaceutica Internazionale SRL, Jan 2021. [Online]. Available: https://www.medicines.org.uk/emc/product/7421/smpc. [Accessed June 2023].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality