East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Avanafil (Spedra®) , new phosphodiesterase-5 inhibitor indicated for the treatment of ED in adult men.
Requested by	Presented to the PCN as a result of horizon scanning

Clinical Effectiveness

For a full evidence review please use the following links:
MTRAC, August 2014,
http://centreformedicinesoptimisation.co.uk/files/Avanafil%20update%20summary%20August%202014.pdf
NICE Advice, ESNM45, August 2014,
http://www.nice.org.uk/Advice/ESNM45
In Summary:
There are no direct head-to-head comparisons of PDE5 inhibitors and indirect comparisons are limited by differences in study design
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
From discussions with Specialists and GPs, the barrier to move all prescribing of PDE5 inhibitors to sildenafil appears to be usefulness of the longer duration of action of tadalafil allowing for more spontaneous intercourse.
Avanafil is faster and longer acting than sildenafil and less expensive than tadalafil, and the committee needs to decide whether there is a place for avanafil in the local health economy. Sildenafil and avanafil absorption is affected by food. This interaction can be a cause of treatment failure and appropriate counselling can improve efficacy. Tadalafil does not interact with food and may be the main reason for it being effective where other PDE5 inhibitors have failed.
It is possible that the relaxation of number of sildenafil tablets which can be supplied may reduce the imperative to have a longer acting PDE5 inhibitor.

Safety

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).
It is not known how the efficacy, tolerability and safety of avanafil compare with the other PDE5 inhibitors

Patient factors

Sildenafil can now be prescribed for all patients with ED for whom there are no contra-indications
Avanafil, tadalafil, vardenafil, and the branded sildenafil may only be prescribed for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIB of the Drug Tariff (Part XIb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed 'SLS'.

Cost implications

Generic Name	Cost per year based on 1 tablet/ week
Sildenafil	£14 - £16
Tadalafil	£350 all doses (Daily tadalafil £712 all doses)
Vardenafil	£183-£305
Avanafil	£142-274

Viagra® and Nipatra® brands of Sildenafil cost (£216 - £306) and (£178-£235) respectively

ED is the most prevalent of the male sexual dysfunctions (prevalence age 30 to 80 years) at 19.2% as compared to 31% for all types of male sexual dysfunction. This equates to about 26 new cases annually per 1,000 men The NHS prescribing restrictions on generic sildenafil have been removed and the DoH has predicted that this is likely to lead to a significant increase in demand for these products. DoH analysis suggests that because generic sildenafil is now much lower than the cost of branded Viagra, even with an increase in demand, the overall cost to the NHS of supplying these products will be less than when they were in-patent with access restrictions in place. Their analysis sets out that following the expiry of Viagra's patent, overall NHS expenditure on ED is expected to reduce from about £144m to £104m a year.

Relevant guidance / reviews

NICE: (Advice ESNM45), http://www.nice.org.uk/advice/esnm45 (See Clinical effectiveness section)
MTRAC: Prescribing Guidance Category B, Avanafil is suitable for prescribing in Primary care under the restrictions imposed by the Department of Health for the funding of drugs for erectile dysfunction
SMC: in the absence of a submission from the holder of the marketing authorisation:
avanafil (Spedra®) is not recommended for use within NHS Scotland (To be submitted in November 2014)
AWMSG: In the absence of a submission from the holder of the marketing authorisation, avanafil (Spedra®) cannot be endorsed for use within NHS Wales for the treatment of erectile dysfunction in adult men. In order for avanafil to be effective, sexual stimulation is required.
European Association of Urology, Guidelines on Male Sexual Dysfunction: Not Discussed

Likely place in therapy relative to current treatments

The European Association Guidelines state that, with regards to '3.5.1.4 Choice or preference between the different PDE5 inhibitors', To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil, and vardenafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it.'

Recommendation to PCN

Options:

1- Reject as there does not appear to be any evidence of superiority to sildenafil, other than onset and duration of action and significantly more expensive to the health economy
2- Approve in second line to sildenafil
3- Approve for initiation by specialists until there is more experience with this medicine

Medicine details	
Name and brand name	Avanafil (Spedra®)
Licensed indication, formulation and usual dosage	Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required Dose range 50-200mg
Summary of mechanism of action, and relevant pharmacokinetics	Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. 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 Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Its pharmacokinetics are dose-proportional over the recommended dose range. Avanafil has a terminal half-life of approximately 6-17 hours
Important drug interactions	According to the summary of product characteristics, avanafil has similar contraindications, cautions and interactions to other PDE5 inhibitors. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4). The concomitant use of potent CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) is associated with increased plasma exposure of avanafil
Monitoring requirements	Monitoring for efficacy and adverse effects only
Prescribing considerations	Recommend Green traffic light status if approved, and not first line treatment which should be sildenafil.
Other considerations	If approved should be used according to ED pathway

References

1. UKMi New Drugs online, accessed October 2014
2. Menarini Farmaceutica Internazionale SRL. Spedra 50 mg, 100 mg and 200 mg tablets, last updated 27-03-2014, Link
3. MTRAC, Commissioning Support for Avanafil, August 2014 Link
4. NICE Advice, ESNM45, Avanafil, August 2014, Link
5.
6. Drug Tariff on-line, accessed November 2014
7. BNF on-line, accessed via www.evidence.nhs.uk, November 2014
8. NICE on-line, accessed November 2014
9. Keele University, Centre for Drug optimisation, Monthly Script, Herefordshire CCG June 2014 Link
10. The British Society for Sexual Medicine (BSSM) Link and
11. European Association of Urology (EAU) Link treatment guidelines for ED
12. Personal Discussions with Mr, Naergar, Frimley Health,
13. Personal discussion with Professor Langley, Dr. Valentine, and Mr Niggam RSCH

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Declaration of interest: None