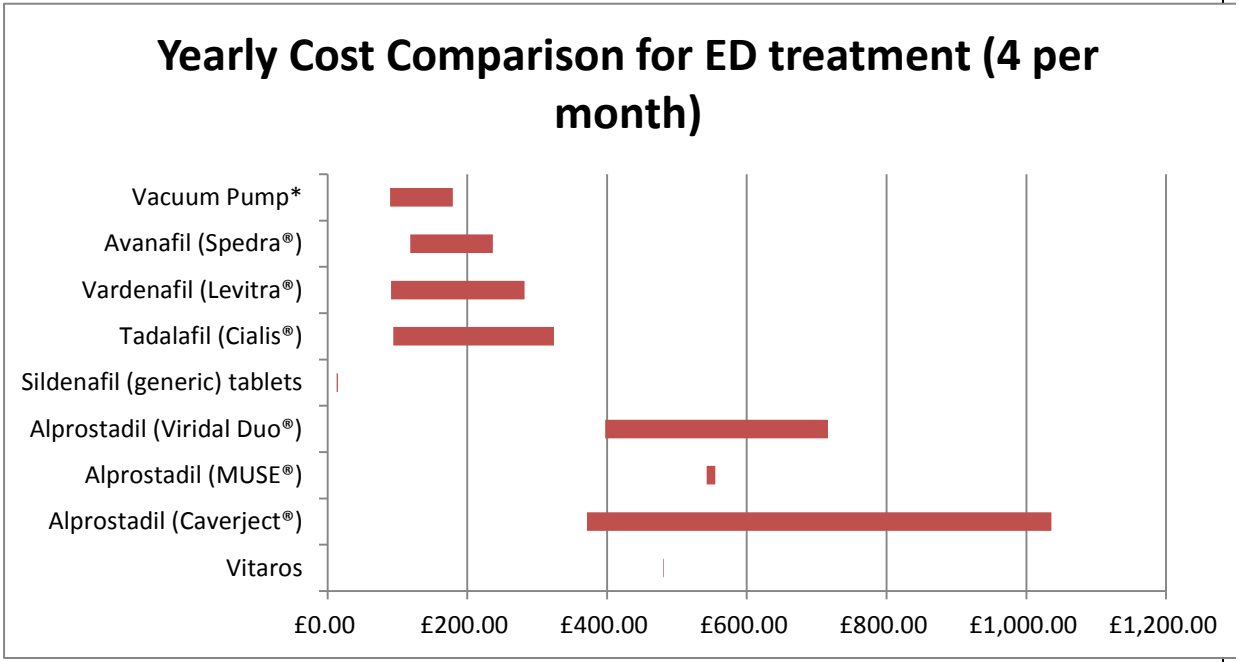
East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Alprostadil, Vitaros® indicated for the treatment of men ≥18 years of age with erectile dysfunction (ED)
Requested by	Identified under Horizon Scanning,

Clinical Effectiveness
This is a new formulation of alprostadil for the treatment of ED. There are already several other formulations approved for use in Surrey as listed on the Surrey PAD: Treatment with prostaglandin E1 INTRACAVERNOSAL INJECTIONS and INTRAURETHRAL INSTILLATIONS are recommended only for the groups of patients identified in the HSC 1999/177 only if oral phosphodiesterase type-5 inhibitors are contraindicated or ineffective at a maximum frequency of dosing of FOUR times per month using the drug with the lowest acquisition cost Green Traffic Light Status These other formulations include the MUSE® and two brands of injections, one of which (Caverject®) is unavailable until at least 2016 The effectivenesss of Vitaros® is reasonable but falls below that seen with transurethral or intracavernosal injection therapy (50% vs 80%) However, for those patients in whom this application is successful, it offers perhaps a less invasive and quicker therapeutic option for the treatment of erectile dysfunction. It is easy to administer and therefore can be prescribed in primary care for those patients after first line trial with PDE5 inhibitors, especially sildenafil.
Safety
Sexual intercourse with a woman of child bearing potential is contra-indicated unless the couple uses a condom barrier Common adverse events include rash, urethral pain, balanitis, pain, erythema and other local reactions
Patient factors
The British Society for Sexual Medicine (BSSM) and the European Association of Urology (EAU) treatment guidelines for ED include various pharmacological, psychological and surgical/mechanical treatments.7 The gold standard treatment for ED is an oral phosphodiesterase 5 (PDE5) inhibitor, such as sildenafil. However, approximately 25% of patients do not respond to a PDE5 inhibitor, and these agents may be contraindicated in others. In cases where PDE5 inhibitors are either ineffective, contraindicated, not used appropriately or have adverse effects, the goal of therapy is to provide the patient with an acceptable alternative option.
Cost implications
If used as second/ third line to sildenafil, it is unlikely to have a cost impact as the costs are

commensurate with existing alternatives. May reduce secondary care referral.



Relevant guidance / reviews

Summarise relevant recommendations or conclusions from
NICE - None
MTRAC - None
SMC - None
AWMSG - None

Likely place in therapy relative to current treatments

This formulation of Alprostadil is less effective than the injection and probably much more acceptable.
There is a strong likelihood that it will not work for at least 50% of patients, however, for the patients who do respond (50% vs placebo 20%) it may have a place in therapy where PDE5 inhibitors have not been effective or tolerated, and before referral to specialists for training to use the injectable formulations.
It does have local side effects, and there is still very little local experience in its tolerability.

Recommendation to PCN

Options for Consideration

1 – Approve for use in patients who have failed on PDE5 inhibitors – Green traffic light status- taking care to evaluate efficacy before long term prescribing

2 – Approve for use in patients who have failed on PDE5 inhibitors – Amber traffic light status- taking care to evaluate efficacy before long term prescribing, until there is more experience in its use

3 – Approve for use in patients who have failed on PDE5 inhibitors – Red traffic light status- taking care to evaluate efficacy before long term prescribing, until there is more experience in its use

4 – Reject

Medicine details	
Name and brand name	Alprostadil, Vitaros®
Licensed indication, formulation and usual dosage	Licensed for the treatment of men ≥18 years of age with erectile dysfunction. Vitaros® is supplied in individual sachets containing one AccuDose™ applicator. Each single applicator contains 300µg alprostadil in 100µl of cream. Each carton contains four applicators Vitaros® is applied to the tip of the penis (meatus) 5-30 minutes prior to attempting intercourse. Do not insert the tip of the AccuDose™ container into the opening of the penis. Use as needed to achieve an erection to a maximum frequency of once every 24 hours and no more than 2-3 times per week.
Summary of mechanism of action, and relevant pharmacokinetics	Alprostadil (PGE1) causes vasodilation of blood vessels in the erectile tissue of the corpora cavernosa, an increase in cavernosal artery blood flow and relaxation of the sinusoidal smooth muscle, resulting in an erection. Alprostadil does not rely on nitric oxide release or an intact nervous system, making it suitable for a range of ED aetiologies which oral therapy does not treat effectively, such as in men with peripheral nerve injury following radical prostatectomy, after spinal cord injuries, severe vascular disease or diabetes with associated neuropathy
Important drug interactions	Potential for interactions with other erectile dysfunction agents, sympathomimetics, antihypertensives, vasodilators, anticoagulants, antiplatelets.
Monitoring requirements	Efficacy and adverse effects
Prescribing considerations	Green traffic light classification
Other considerations	Only recommended only for the groups of patients identified in the HSC 1999/177 only if oral phosphodiesterase type-5 inhibitors are contraindicated or ineffective at a maximum frequency of dosing of FOUR times per month

Potential patient group	
Brief description of disease	A large-scale community study showed that 52% of men (aged 40 to 70 years) were affected at some time (mild 17%; moderate 25%; severe 10%). About 40% of men at age 40 may suffer some form of erectile dysfunction.
Potential patient numbers per 100,000	Study equates to about 26 new cases annually per 1,000 men. Approximately 25% of patients with ED do not respond or tolerate PDE5 inhibitors
Outcomes required	Penile erection sufficient for satisfactory sexual performance

Summary of current treatment pathway
The British Society for Sexual Medicine (BSSM) Link and European Association of Urology (EAU) Link treatment guidelines for ED

Evidence review

This is not a new drug, just a new formulation. Trials carried out were short term with open label extensions. Trials did include patients with co-morbidities, including diabetes, cardiovascular disease, prostatectomy and hypertension They also included a proportion of patients who failed to respond to prior sildenafil therapy (19%)
The SmPC comments that Vitaros has been evaluated in 2 double-blind, placebo-controlled phase 3 studies, with statistical superiority demonstrated over placebo for primary outcomes relating to erectile function domain scores, vaginal penetration and ejaculation. The regulatory assessment report states that the absolute size of the favourable changes induced by treatment was 'modest', although a clinically relevant response was found in about 40% of the patients. Direct comparisons with PDE-5 inhibitors are not available; indirect comparisons indicate a much lower effect for Vitaros than PDE-5 inhibitors. Comparison with other alprostadil-containing products is hampered by the use different efficacy measures and the lack of direct comparative trials; however, the assessment report comments that the mode of application for Vitaros is superior to other alprostadil treatments.

Equity / Stakeholder views

Decisions of local Trusts DTCs and neighbouring APCs	
Recommendations from national / regional decision making groups	
Stakeholder views	
CCG priorities	

References

1. Takeda UK Ltd. Vitaros® 3mg/g cream Summary of Product Characteristics; last updated Oct 2014 Link
2. Topical Alprostadil Cream Formulary Pack, Takeda
3. UKMi, New Drugs on-line, accessed, November 2014
4. Drug Tariff on-line, accessed November 2014
5. BNF on-line, accessed via www.evidence.nhs.uk, November 2014
6. NICE on-line, accessed November 2014
7. Keele University, Centre for Drug optimisation, Monthly Script, Herefordshire CCG June 2014 Link
8. The British Society for Sexual Medicine (BSSM) Link and
9. European Association of Urology (EAU) Link treatment guidelines for ED
10. Personal Discussions with Mr, Naergar, Frimley Health,
11. Personal discussion with Professor Langley, Dr. Valentine, and Mr Niggam RSCH

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Declaration of interest: None