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Bedfordshire and Luton Joint Prescribing Committee

Published December 2019
Review: December 2022

Aviptadil / phentolamine Intracavernosal Injection (Invicorp) for Erectile Dysfunction

Formulary Status: Amber :-	**For Specialist initiation , GP continuation**

JPC Recommendation:

- The committee agreed to support the addition of Aviptadil/ phentolamine (Invicorp) intracavernosal Injection to the Befordshire and Luton Joint Formulary for the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology as a second line agent for use in those who have failed on oral therapies (oral PDE5 inhibitors).
- Prescribing of Aviptadil / phentolamine (Invicorp) intracavernosal injection must be initiated by a Specialist (Urologist) and may be continued by GPs.

Ref : JPC Bulletin 284

Bedfordshire CCG
Luton CCG

New Medicine Review

Aviptadil 25mcg / phentolamine mesilate 2mg (Invicorp) solution for intracavernosal injection

Medicine	Aviptadil 25mcg / phentolamine mesilate 2mg (Invicorp) solution for intracavernosal injection
Document status	Final
Date of last revision	N/A
Proposed Sector of prescribing	Specialist initiation by a Urologist and continuation in primary care
Introduction **Summary Key points** **Evidence level**	**Introduction** Erectile dysfunction (ED) is a very common condition, particularly in older men. It is estimated that half of all men between the ages of 40 and 70 will have it to some degree. ED has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance. Although ED is not perceived as a life-threatening condition, it is closely associated with many important physical conditions and may affect psychosocial health. As such, ED has a significant impact on the quality of life of patients and their partners. The Luton & Dunstable Hospital has requested the addition of aviptadil/ phentolamine (Invicorp) intracavernosal injection for the treatment of erectile dysfunction (ED) (in accordance with the marketing authorisation for Invicorp) to be added the Joint Bedfordshire and Luton Formulary as an alternative treatment option to alprostadil intracavernosal injection (Caverject). One reason for the request has been due to intermittent supply problems with alprostadil (Caverject). The other reason is that aviptadil / phentolamine is much easier to initiate than Caverject as no dose titration is needed. Only one hospital visit is therefore required rather than 3 for Caverject. **Key Points:** The British Society for Sexual Medicine “Guidelines for the management of erectile dysfunction” was last updated in 2017. With respect to pharmacological treatment of non-reversible erectile dysfunction, phosphodiesterase type-5 inhibitors (PDE5 inhibitors) are first-line options. A patient should take eight doses of PDE5 inhibitor at the maximum dose before being classed as a non-responder. Second-line treatments are intracavernous injection therapy, intraurethral alprostadil or topical alprostadil (with a skin penetration enhancer). The Scottish Medicines Consortium (SMC) has approved of aviptadil/ phentolamine (Invicorp) for restricted use within NHS Scotland for the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology. It has been approved for use in those who have failed on oral therapies (oral PDE5 inhibitors) and other non-injectable formulations of erectile dysfunction medications.

	Approximately 25% of patients do not respond to PDE5 inhibitors so require alternative treatments. When oral medicines have failed, other options for treatment include injections, vacuum pump therapy or penile implants which require surgery. Current injections can be painful to the point where men have to stop treatment. Men who have used aviptadil/phentolamine consulted by the patient groups, reported that it causes less pain and discomfort than other comparable options. The prospect of being able to access aviptadil/phentolamine when other treatments have not worked, is important to patients and their partners as it provides an opportunity to increase quality of life without recourse to more invasive options. In an open-label, crossover study of men with non-psychogenic erectile dysfunction, aviptadil / phentolamine injection was compared with a prostaglandin-based intracavernosal injection. Patients who achieved an erection suitable for sexual intercourse (grade 3) from both treatments were entered into a comparative phase in which similar proportions of injections of each treatment resulted in grade 3 erections. Aviptadil / phentolamine injection was associated with a lower incidence of moderate or severe adverse events and pain when compared with the prostaglandin injection. This review outlines the key evidence of efficacy, safety and cost for aviptadil/ phentolamine and is mainly based on the review by the Scottish Medicines Consortium (SMC) published November 2017.[1]
The intervention Mechanism of action	Aviptadil is vasoactive intestinal polypeptide, a neurotransmitter with a regulatory role in the control of smooth muscle activity in the male urogenital canal. It relaxes cavernosal smooth muscle and may have a veno-occlusive action. Phentolamine is an alpha-adrenoceptor antagonist which causes vasodilatation and also independently relaxes smooth muscle. The combination treatment leads to penile tumescence following sensory stimulation.
Licensed indication	For the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology.
Formulation/Available Products	Solution for injection presented in a glass ampoule with syringe and needle (various pack sizes including single).
Usual dosage	The contents of one ampoule (aviptadil 25 micrograms / phentolamine 2mg) should be administered by direct intracavernous injection. Injection frequency should not exceed once daily or 3 times weekly. Initial injections must be administered by medically trained personnel, and after proper training, aviptadil / phentolamine may be injected at home. It is recommended that the patient is regularly monitored (e.g. every 3 months) particularly in the initial stages of self-injection therapy.
Treatment alternatives/ place in therapy	Current standard of care/comparator therapies: Alprostadil (Caverject) powder and solvent for solution for injection. Caverject requires a minimum of 3 attendances for titration of dose (titration dosing schedule slightly different when considering erectile dysfunction associated with neurological dysfunction).

	Intracavernosal injections are recommended as second-line treatments after phosphodiesterase type-5 inhibitors (PDE5I) e.g. sildenafil). The specialist has requested aviptadil / phentolamine be added to the formulary in part due to on-off drug shortages of alprostadil (Caverject). The other reason is that aviptadil / phentolamine is much easier to initiate than Caverject as no dose titration is needed. Only one hospital visit is therefore required rather than 3 for Caverject.
Future alternatives	
National guidance	NICE has not issued any guidance on inttracavernosal injections. The British Society for Sexual Medicine "Guidelines for the management of erectile dysfunction" was last updated in 2017. With respect to pharmacological treatment of non-reversible erectile dysfunction, PDE5 inhibitors are first-line options. A patient should take eight doses of PDE5 inhibitor at the maximum dose before being classed as a non-responder. Second-line treatments are intracavernous injection therapy, intraurethral alprostadil or topical alprostadil (with a skin penetration enhancer). The Scottish Medicine Consortium (SMC) has also issued guidance and has approved its use in those who have failed on oral therapies (oral phosphodiesterase type-5 inhibitors) and other non-injectable formulations of erectile dysfunction medications. The European Association of Urology updated its guidance on Male Sexual Dysfunction in 2016. This also places intracavernosal injections as a second line option after PDE-5I.
Local Guidance	None for L&D hospital. Follow British guidelines.
Evidence for use	From the SMC review as no new evidence has been identified: The main study (VP007) was a multi-centre, open-label crossover study to investigate tolerability, efficacy and patient preference of intracavernosal injections of aviptadil / phentolamine and alprostadil. The study recruited men (>18 years of age) in a stable heterosexual relationship, and who had erectile dysfunction for at least one year. Men with erectile dysfunction of psychogenic aetiology were excluded.[4] The study comprised two phases. In the dose-finding phase (phase 1), patients (n=187) started on the lowest dose of study treatment which was escalated until a grade 3 erection (erection suitable for sexual intercourse) was achieved. The patient then crossed-over to use the other study treatment and escalate dose to response. The order of study treatment was allocated by randomised assignment. Patients who achieved a grade 3 erection with both treatments in phase 1 were eligible to enrol in phase 2. In phase 2, patients received four doses of each treatment at the effective doses identified in phase 1. The order of use was determined by randomisation; patients crossed-over after using four doses of the randomly assigned treatment. Four doses of aviptadil /

phentolamine formulated in auto-injectors were then given to patients subsequent to completion of the other two treatments.[4]

Table 1: Doses used in the pivotal study

	aviptadil / phentolamine ampoules	**alprostadil ampoules**	**aviptadil / phentolamine auto-injector**
Phase 1	12.5 micrograms / 0.5mg 25 micrograms / 1mg 25 micrograms / 2mg	5 micrograms 10 micrograms 15 micrograms 20 micrograms	not used
Phase 2	Dose in phase 1 that achieved a grade 3 erection		

Patient diaries were completed to record adverse events (AEs) and the duration and strength of erection. The strength was graded on a four-point scale (0= no erection, 1= swelling, 2= partial erection, 3= erection suitable for sexual intercourse). Any discomfort associated with erections were scored with a five-point scale (none, mild, moderate, severe and unacceptable). In addition to patients recording AEs in a diary, investigators conducted a full examination at baseline and final visit, to screen for any other AEs.4

In phase 1, a grade 3 erection was achieved in significantly fewer patients injected with aviptadil / phentolamine (73%, 137/187) when compared with alprostadil (83%, 155/187), p=0.002. Of the 130 patients who achieved a grade 3 erection with both treatments in phase 1, 107 entered phase 2. Response rates in phase 2 were reported as a proportion of the number of injections administered, table 2; response to the unlicensed auto-injectors is not presented.

Table 2: Response rate to ampoules in phase 2 of the study4

	aviptadil / phentolamine ampoules	**alprostadil ampoules**
Total injections given	395	380
% achieving a grade 3 response	84%	83%

Patient preference was assessed in both phases of the study. A low proportion of patients who completed phase 1 of the study, 39% (51/130) provided patient preference data. A greater proportion of patients preferred aviptadil / phentolamine than alprostadil (69% versus 31%, p=0.011). In phase 2 patient preference data for the 67 patients who used all 12 doses of injection (four aviptadil /phentolamine ampoules, four alprostadil ampoules, and four aviptadil / phentolamine auto-injector) were reported. Patients preferred the auto-injector formulation overall; a significantly greater proportion preferred the aviptadil / phentolamine ampoules over the alprostadil ampoules.4

Safety*

According to the SPC approximately 10% of patients experience adverse reactions. Flushing is often observed but is rarely problematic and may be difficult to distinguish from the flushing associated with intercourse. Haematoma and bruise may occur at the injection site. This will become

	less of a problem when patients become more experienced in the injection technique itself. Invicorp is contraindicated in patients taking heparin or oral anticoagulants. Other contraindications are the same as with alprostadil.
Costs **Tariff status** **Activity costs**	<table><tr><th>Drug & Dosage</th><th>30 day cost/per patient</th><th>Annual Cost per patient</th></tr><tr><td>Aviptadil / phentolamine</td><td>£38</td><td>£494</td></tr><tr><td>Alprostadil vials Usual dose 5 to 20 mcg by intracavernous injection</td><td>£36.90 to £52.40</td><td>£480 to £681</td></tr><tr><td>Alprostadil dual chamber. Usual dose 5 to 20 micrograms by intracavernous injection</td><td>£29.40 to £38</td><td>£382 to £494</td></tr></table> **N.B.** Doses are for general comparison and do not imply therapeutic equivalence. *Costs calculated using the full cost of vials/ampoules assuming wastage and based on 52 doses per year.* Prices from on-line Drug Tariff or on-line BNF
Cost effectiveness (if available)	**From the SMC review:** The submitting company presented a cost-minimisation analysis (CMA) comparing aviptadil / phentolamine to alprostadil in adult males who suffer from erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed aetiology, and have failed on oral therapies (oral PDE5-inhibitors) and other non-injectable formulations of erectile dysfunction medications. SMC clinical experts have indicated that the comparator is appropriate for the patient population of interest. The time horizon for the analysis was one year. The evidence to support clinical equivalence of treatments, as necessary for a CMA, was the VP007 study. The submitting company assumed that while treatments were equally efficacious in achieving the outcome of treatment, the adverse event profile differed and therefore included resource use relating to treatment of higher rates of priapism and penile fibrosis with alprostadil within the analysis. The only other resource use in the model related to the costs associated with initial consultant outpatient appointments for titration; one visit was assumed for aviptadil / phentolamine compared to three for alprostadil. It was assumed that both treatments would be given once weekly, and it was also assumed that for alprostadil the initial titration treatments would be given using the dual chamber formulation, whereas ongoing weekly treatment would be using 20 microgram vials. The base case result was that aviptadil / phentolamine was the cost-minimising treatment with savings of £411.24 per patient per year (total costs: £627.20 v £1038.44). The savings associated with aviptadil /

	phentolamine comprised reduced medicines acquisition costs of £142, reduced titration visit costs of £200 and reduced costs associated with adverse events of £69. A range of one-way and scenario based sensitivity analyses were presented and these showed that the results were most sensitive to the assumptions made in relation to titration visits (frequency and unit cost). However, in all scenarios presented by the company, aviptadil / phentolamine remained costsaving. The lowest saving was £150 when it was assumed that alprostadil only required 1.67 titration visits. There were a number of weaknesses associated with the analysis: • The clinical evidence to support equivalence of treatments to justify the choice of a cost-minimisation analysis was not specifically in the patient population proposed by the company. As noted above, there were also other weaknesses associated with the clinical evidence base. As such, there is uncertainty associated with the clinical data underpinning the economic analysis. • The cost-minimisation analysis included differences in adverse event rates, with these being informed by clinical expert opinion. Technically, for a cost-minimisation analysis, the treatments should be equivalent on all outcomes and thus the differences in adverse events should not be assumed in the analysis. However, removal of these differences would not alter the finding of cost-minimisation in favour of aviptadil / phentolamine; if all adverse events were removed from the analysis, the cost-saving reduced to £342. • The analysis assumed that a more expensive form of alprostadil was used for weekly treatment than the form used in the initial titration phase of the patient's care. This seemed an unusual assumption which lacked credibility with SMC clinical experts, and would bias the analysis in favour of aviptadil / phentolamine. Using the dual chamber formulation for both treatment initiation and ongoing maintenance treatment resulted in a lower cost-saving than in the base case of £296. • The analysis was sensitive to the assumptions used regarding the number of titration visits needed for alprostadil. SMC clinical experts have been asked to comment on this aspect and noted that the assumptions used could overstate the requirements for alprostadil, particularly because treatment initiation could be offered by nursing staff rather than a consultant. • The company was asked to provide some additional sensitivity analysis combining a range of alternative assumptions to take account of the uncertainties noted above. Removing costs associated with adverse events, equalising titration visit costs and using the dual chamber formulation of alprostadil for all phases of treatment reduced the overall cost-saving associated with aviptadil / phentolamine to £14. Despite these issues, the economic case was considered demonstrated.
Potential number of patients in	The requesting specialist (from the Luton & Dunstable Hospital) has indicated that this drug may be useful in up to 300 patients per year (out of the 1000+ patients treated for ED). Invicorp is fairly cost-comparable but it

Bedfordshire and Luton Impact per 100,000 population **Affordability considerations**	depends on what doses of Caverject would be needed and what presentation is used (i.e. Caverject Dual or vials). Invicorp could provide savings of up to £56,000 per annum (compared with high dose Caverject vials) or cost an additional £33,600 (when compared with lower doses of Caverject Dual) based on drug acquisition costs alone. However, there are savings from not requiring 3 dose titration visits (only one appointment required). Please see the SMC cost-minimisation analysis above for further information. Any costs/usage associated with use of the drug at Bedford Hospital would be additional to these usage/cost estimates.
Decisions from other bodies **Comments sought from –**	
Evidence strengths and limitations	Limitations: • SPC not available on eMC (search via MHRA website) • Relatively small patient populations/sub-populations • Various unlicensed doses and formulations of aviptadil / phentolamine used in trials • Very little clinical trial data looking at efficacy of Invicorp in alprostadil non responders. • Study designs not adequately described • Reasons for patients leaving studies not adequately explained.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1- Search Strategy

NICE Evidence search – October 2019

Embase search – November 2019

References:

1. November 2017; Scottish Medicine Consortium. SMC No 1284/17. Aviptadil / phentolamine 25 micrograms / 2mg solution for injection (Invicorp®)
2. Summary of Product Characteristics: Invicorp. Date of revision of text 13/09/2017. Accessed via MHRA website (https://www.gov.uk/pil-spc).
3. Hackett G, Kirby M, Wylie K, et al. British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction in Men—2017. J Sex Med 2018; 15:430–457.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*