SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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aviptadil / phentolamine 25 micrograms / 2mg solution for injection (Invicorp®)

SMC No 1284/17

Evolan Pharma AB

10 November 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

aviptadil / phentolamine (Invicorp®) is accepted for restricted use within NHS Scotland.

Indication under review: For the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology.

SMC restriction: for use in those who have failed on oral therapies (oral phosphodiesterase type-5 inhibitors) and other non-injectable formulations of erectile dysfunction medications.

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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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Indication

For the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology.[1]

Dosing Information

The contents of one ampoule (aviptadil 25 micrograms / phentolamine 2mg) should be administered by direct intracavernous injection.

The injection should provide the patient with an erection that is satisfactory for sexual intercourse. It is recommended that the duration of the erection does not exceed one hour. 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.[1]

Product availability date

November 2015

Summary of evidence on comparative efficacy

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.[1-3]

The submitting company has requested that SMC considers aviptadil / phentolamine when positioned for use in those who have failed on oral therapies (oral phosphodiesterase type-5 [PDE5]-inhibitors) and other non-injectable formulations of erectile dysfunction medications.

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 study[4]

	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]

Summary of evidence on comparative safety

In both phases of the study, AEs were experienced in fewer patients when using aviptadil / phentolamine (30% in phase 1 and 30% in phase 2 when using the ampoule preparation) when compared with alprostadil (46% in phase 1 and 46% in phase 2) injections.[4]

The study's sample size was based on the proportion of patients reporting moderate or severe adverse events. Moderate adverse events were defined as being of sufficient effect to interfere with daily activity or requiring simple treatment; severe adverse events prevented usual activity or were incapacitating. Moderate or severe AEs occurred in fewer patients when taking aviptadil / phentolamine versus alprostadil; in phase 1 the respective proportions were 4.3% (8/187) and 12% (23/187). In phase 2 the proportions were 5.6% (6/107) and 14% (15/107) respectively.[4]

When moderate or severe AEs were quantified by number of injections in phase 2, there were significantly fewer AEs when using aviptadil / phentolamine ampoules (4 per 100 injections per patient) when compared with alprostadil (13 per 100 injections per patient), p=0.049.[4]

Comparisons of AEs were conducted on injections administered during phase 2 of the study. Aviptadil / phentolamine injections (ampoules or autoinjector) were associated with significantly lower incidence of pain upon injection when compared with alprostadil; 3% versus 28% of injections, p<0.001.

There was a significantly greater incidence of facial flushing; 16% (when using aviptadil / phentolamine ampoules) versus 3% of alprostadil injections, respectively, p<0.001. Bruising was infrequent and similarly incident between treatments; 1% of aviptadil / phentolamine (when using ampoules) and 4% of alprostadil injections. Bleeding occurred in 1% of injections in both treatment groups. There were no cases of priapism reported.[4]

Four patients withdrew from the study due to an adverse event; it was not reported what treatments patients were taking at the time of withdrawal, or if the adverse events were considered to be treatment-related.[4]

Summary of clinical effectiveness issues

Erectile dysfunction is defined as "the persistent inability to attain and / or maintain an erection sufficient for sexual performance".[5] The prevalence of erectile dysfunction increases with age and the pathophysiology may be psychogenic, drug-induced (e.g. antihypertensive agents, antidepressants), hormonal (e.g. hypogonadism, hyperprolactinaemia), anatomical, neurogenic (e.g. stroke, diabetes mellitus), or vasculogenic (e.g. smoking, cardiovascular disease).

In patients with non-reversible erectile dysfunction, lifestyle advice, vacuum erection devices and oral PDE5 inhibitors are first-line treatment options.[5, 6] In patients for whom PDE5 inhibitors are not appropriate, or have not responded to this first-line therapy (when taken correctly and for six to eight attempts at maximum dose), then second-line pharmacological options include intracavernosal injections of alprostadil, intraurethral or topical alprostadil.[5,6] European guidelines recommend intracavernosal injection as a second-line option. Intraurethral alprostadil is recommended as an alternative to intracavernosal injection, for patients who wish to have a less invasive, but less effective treatment.[6] Treatments for erectile dysfunction in NHS Scotland are subject to prescribing restrictions outlined in the Scottish Drug Tariff.[7]

The submitting company has requested that SMC considers aviptadil / phentolamine when positioned for use in those who have failed on oral therapies (oral PDE5-inhibitors) and other non-injectable formulations of erectile dysfunction medications. Clinical experts consulted by SMC advised that the most relevant comparator treatment is alprostadil intracavernous injection.

In the key study significantly fewer patients reported moderate or severe AEs when taking aviptadil / phentolamine when compared with alprostadil. There was a lower incidence of pain when patients administered aviptadil / phentolamine when compared with alprostadil.[4]

The main efficacy outcome was a direct health outcome for patients with erectile dysfunction. In the dose-finding phase of the key study, aviptadil / phentolamine injection resulted in significantly fewer patients achieving an erection suitable for sexual intercourse when compared with alprostadil injection. No statistical comparison of response rates was conducted in the second-phase of the study though response rates were numerically similar.[4]

The proportion of patients who used the licensed dose in the second phase was not reported; neither response rates or safety outcomes for aviptadil / phentolamine 25 micrograms / 2mg were reported separately.[4] It may be reasonable to extrapolate that response with lower doses is likely to lead to response with the licensed dose; however relative safety of the licensed dose of aviptadil / phentolamine is not known.

Sources of bias which may limit the internal validity of the key study include the incomplete accounting of patient disposition through the phases of the study. Reasons for patient drop-out were not adequately reported. Patient preference outcomes should be interpreted cautiously; the study was open-label and a small proportion of study participants provided preference data (39% of patients in the dose-finding phase, and only patients who administered all 12 injections in the second phase). Not all outcomes were reported; duration of erection, recorded in patient diaries, were not presented.[4]

The generalisability of the key study is limited by the mismatch of the study population with the population eligible for the indication under review. There was no specific eligibility criteria in relation to previous failure or lack of suitability for PDE5 inhibitors and baseline characteristics did not report upon patients' previous use of erectile dysfunction treatments.[4]

The aviptadil / phentolamine auto-injector device used in the second phase of the study is not marketed; patient-preference for this device cannot be extrapolated to the licensed presentation. Furthermore the preference results may not generalise to use of alprostadil dual chamber devices; ampoules were used in the study.

The dose-finding phase allowed titration of alprostadil from 5mg to 20 micrograms.[4] Depending upon the aetiology, initial doses of 1.25 or 2.5 micrograms are recommended, and while the majority of patients will respond within the dose range 5 to 20 micrograms, doses up to 60 micrograms can be given.[8,9] The relative effectiveness of aviptadil / phentolamine and alprostadil may not have been fully captured in the study. Response rates in the second phase of the study may over-estimate those achieved in practice; this was an enriched population who had previously demonstrated efficacy to the study treatments.

No evidence was presented for men with psychogenic erectile dysfunction. VP007 excluded men with any overt psychogenic aetiology. The study also excluded men with known systemic disease associated with overall weakness.[4] Part 12 of the current Scottish Drug Tariff describes the certain circumstances in which medicines for erectile dysfunction can be prescribed in the NHS.[7] Some of the circumstances listed are systemic diseases which can be associated with overall weakness (e.g. multiple sclerosis, poliomyelitis). These patient groups who would be eligible for treatment in NHS Scotland may have been excluded from the study.

Compared with alprostadil injection, titration of dosage of aviptadil / phentolamine is not required; identification of non-responders can be made more rapidly, and alternative options offered sooner. As with all intracavernosal injections, patient education for appropriate timing of dosage, preparation and administration, and advice on managing complications requires specialist input. The introduction of aviptadil / phentolamine is unlikely to have any major service implications.

Summary of comparative health economic evidence

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 cost-saving. 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.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Prostate Cancer UK and Prostate Scotland, both are registered charities.
- Prostate Cancer UK has received less than 0.01% pharmaceutical company funding in the past two years, with none from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years.
- Erectile dysfunction (ED) is closely associated with many physical conditions such as prostate cancer, multiple sclerosis and diabetes. Treatment–related ED affects a substantial number of men with prostate cancer and benign prostatic hyperplasia. The biggest challenges of living with ED are the strain on psychological and psychosexual health and the consequent relationship issues.
- 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.

Additional information: guidelines and protocols

The European Association of Urology updated its guidance on "Male Sexual Dysfunction" in 2016.[6] In general, erectile dysfunction can be successfully treated with currently available treatment options. It can be cured in specific clinical cases such as psychogenic erectile dysfunction, post-traumatic arteriogenic erectile dysfunction in young patients, and hormonal causes (eg hypogonadism, and hyperprolactinaemia). Treatment options should be selected based on patient and partner satisfaction, quality of life factors in addition to treatment-related efficacy and safety.

- Risk factor modification and lifestyle changes should precede or accompany pharmacological treatment.

- PDE5 inhibitors are first-line pharmacological treatment
    - Failure to respond to PDE5 inhibitors is usually due to incorrect use (eg poor patient education like incorrect timing of dosage in relation to sexual activity) or lack of efficacy.
    - An adequate trial of six attempts with a medicine is recommended.
    - There is limited data to suggest patients may respond better to one PDE5 inhibitor than to another.
- Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED.
- Use intracavernous injections as second-line therapy.
    - The success rate can be as high as 85%
    - Injection technique training is required.
    - There can be a drop-out rate of 41 to 68%; most drop-outs happen in the first two to three months of therapy.
- Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less efficacious treatment.

At the time of preparation, aviptadil plus phentolamine was only licensed in Scandinavia. The guideline notes that clinical studies showed that the combination is an effective treatment in over 80% of men with erectile dysfunction, including those who had failed other therapies; however, when compared with existing intracavernous injections, it is associated with a very low incidence of penile pain and very low risk of priapism.

The British Society for Sexual Medicine "Guidelines for the management of erectile dysfunction" was last updated in 2013.[5] 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).

Additional information: comparators

Alprostadil intra-cavernous injection.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
aviptadil / phentolamine	**25 micrograms / 2mg by intracavernous injection**	**494**
alprostadil vials	Usual dose 5 to 20 micrograms by intracavernous injection	480 to 621
alprostadil dual chamber	Usual dose 5 to 20 micrograms by intracavernous injection	382 to 494

Doses are for general comparison and do not imply therapeutic equivalence. Medicine costs from eVadis on 03 August 2017, except aviptadil / phentolamine (from MIMS online on 28 August 2017). Costs calculated using the full cost of vials/ampoules assuming wastage and based on 52 doses.

Additional information: budget impact

The submitting company estimated there would be 28,986 patients eligible for treatment with aviptadil / phentolamine in year 1 rising to 29,333 patients in year 5. The estimated uptake rate was 10% in year 1 (2,435 patients) and 30% in year 5 (7,392 patients) with a discontinuation rate of 16% applied. Information from SMC clinical experts suggest that these figures may be an over-estimate of likely patient numbers.

The gross impact on the medicines budget was estimated to be £1.23m in year 1 rising to £3.73m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £346k in year 1 rising to a saving of £1.05m in year 5. The net budget impact estimates were based on use of alprostadil 20 microgram vials; use of the dual chamber formulation would have resulted in much lower net savings.

References

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This assessment is based on data submitted by the applicant company up to and including 10 October 2017

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local

use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.