

HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC)

AVIPTADIL/PHENTOLAMINE SOLUTION FOR INJECTION FOR SYMPTOMATIC TREATMENT OF ERECTILE DYSFUNCTION (ED) IN ADULT MALES

RECOMMENDED FOR RESTRICTED USE (AMBER INITIATION)

Name: generic (trade)	What it is	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Aviptadil 25microgram/ Phentolamine 2mg (Invicorp®)	Fixed dose combination of a short acting alpha-blocker and a vasoactive intestinal polypeptide	Licensed for treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic or mixed aetiology	June 2019	Final	<ul style="list-style-type: none"> NICE TA: not available SMC recommended AWMSG recommended

HMMC recommendation:

Aviptadil 25microgram/Phentolamine 2mg solution for injection, within licensed indications, **is recommended for restricted use** as an intracavernosal option for the treatment of ED for patients who have a contra-indication, intolerance or treatment failure on oral PDE-5 inhibitors. **FOR INITIATION BY SPECIALIST.** Specialist team undertake initial injection, patient training on the correct injection technique, advise on monitoring aspects and action to take in case of adverse events. Once stabilised and confirmation of benefit, for continuation in primary care.

- The recommendation excludes penile rehabilitation following prostate surgery
- Prescribing restricted in line with SLS* criteria (local recommendation) (*SLS= *Selected List Scheme notes drugs that may only be ordered under certain circumstances on the NHS, as specified in Drug Tariff. Most drugs for treatment of erectile dysfunction fall under this category*)

Background Information:

- Aviptadil 25micrograms/phentolamine 2mg solution for injection (Invicorp®) is a fixed dose therapy combination licensed for treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic or mixed aetiology. Phentolamine is a short-acting alpha-adrenoceptor antagonist causing vasodilation. It also has a direct effect on smooth muscle causing relaxation. Aviptadil is a vasoactive intestinal polypeptide. It relaxes cavernosal smooth muscle and may have a veno-occlusive action.
- Invicorp® should be administered by direct intracavernous injection. It is a fixed dose treatment option that does not require dose titration.
- Unlike alprostadil, sexual stimulation is required to provide optimal erection.
- Injection should not exceed once daily or 3 times weekly. The initial injection must be administered by medically trained staff. Correct injection technique is important and only after training can injections be administered at home.
- Especially during initial phase of treatment, regular monitoring is required (e.g. 3 monthly). Careful examination of the penis is recommended to detect signs of penile fibrosis or Peyronie's disease - discontinue treatment in patients who develop penile angulation, cavernosal fibrosis or Peyronie's disease
- It requires fridge storage and has a shelf life of 9 months. The ampoule may be used directly from the fridge or can be brought to room temperature prior to injection
- The Summary of Product Characteristics notes that approximately 10% of patients may experience adverse reactions. Mild transient flushing of the face or trunk occurs commonly. It is rarely problematic. If associated with discomfort, palpitations or tachycardia it may require treatment withdrawal. Haematoma and bruising can occur at the injection site. This will become less of a problem as patients become more experienced in the injection technique. Priapism may occur. Patients must immediately report to a physician if it lasts for a prolonged period. Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules & peyronie's disease may occur following intracavernosal administration. Pain post injection is described as rare ($\geq 1/10000$ to $< 1/1000$).
- Invicorp® is available in a container of 5 syringes x 0.35ml £47.50 (1syringe = £9.50, *Drug Tariff May 19*)

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness:

Evidence on aviptadil 25micrograms/phentolamine 2mg is largely derived from one study (VP007), comparing aviptadil/phentolamine with alprostadil. The study was an open-label, multicentre randomised crossover study designed to

- Compare efficacy and tolerability of aviptadil/phentolamine and alprostadil
- Evaluate patient preference for these treatments.

The study consisted of two phases.

Phase 1 was a dose-finding phase, used to establish the doses of aviptadil/phentolamine and alprostadil required to achieve a grade 3 erection (grade 3 erection = an erection suitable for sexual intercourse) in each patient. Patients who did not achieve an adequate response to either treatment were not eligible for phase 2 of the study.

Phase 1 clinical outcomes: In phase 1, 187 patients received treatment. Significantly fewer patients achieved a grade 3 erection after treatment with aviptadil/phentolamine (137/187 (73%)) than after treatment with alprostadil (155/187 (83%)) (P=0.002). (Grade 3 erections are reported *per patient* in this phase)

Patient treatment preference was reported for 51/130 (39%) of patients. A greater proportion of patients preferred aviptadil / phentolamine than alprostadil (69% versus 31%, p=0.011).

In phase 2, the comparative phase, patients received each treatment at the dose at which they had achieved a response in phase 1. Each patient was issued with four doses of aviptadil/phentolamine presented as ampoules and four doses of alprostadil presented as powder for injection; the order in which patients received these was randomised. Additionally, each patient received four doses of aviptadil/phentolamine presented in an auto-injector, for use after completion of the other two treatments. In both phases, efficacy was determined using information provided by patients, which had been recorded in a diary.

Phase 2 clinical outcomes: Phase 2 included 107 patients. Grade 3 erections are reported in terms of the *total number of injections*. The percentage of injections resulting in a grade 3 erection were 83%, 84% and 85% with alprostadil, aviptadil/phentolamine ampoules and aviptadil/phentolamine auto-injector respectively.

Patient treatment preference was reported for 67 patients in phase 2. Significantly more patients preferred one of the aviptadil/phentolamine preparations over alprostadil. Noting that 73% of patients preferred the aviptadil/phentolamine auto-injector preparation (not currently licensed in the UK), whilst 19% preferred the licensed aviptadil/phentolamine ampoules preparation and 8% preferred alprostadil.

Safety:

The VP007 study notes:

Adverse events of discomfort associated with erections: Patient diaries were completed to record adverse events (AEs). 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.

AEs were experienced in fewer patients when using aviptadil / phentolamine (30% in phase 1, 30% in phase 2 when using the ampoule preparation) when compared with alprostadil (46% in phase 1 and 46% in phase 2) injections. Four patients withdrew from the study due to an adverse event.

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.

(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)

Comparisons of AEs were conducted on injections administered during phase 2 of the study.

Pain on injection: 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.)

Facial flushing: Significantly greater incidence of facial flushing when using aviptadil / phentolamine ampoules) 16% versus 3% of alprostadil injections. (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.

The Summary of Product Characteristics (SPC) notes that approximately 10% of patients may experience adverse

reactions. Mild transient flushing of the face or trunk occurs commonly. It is rarely problematic. If associated with discomfort, palpitations or tachycardia it may require treatment withdrawal. Haematoma and bruising can occur at the injection site. This will become less of a problem as patients become more experienced in the injection technique. Priapism may occur. Patients must immediately report to a physician if it lasts for a prolonged period. Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules and peyronie's disease may occur following intracavernosal administration.

Adverse reactions and precautions for use of comparative treatment alprostadil appear much more extensively documented in the corresponding datasheet. However focussing on penile pain, one of the claimed benefits of Invicorp[®], the most frequent adverse reaction after intracavernosal injection of alprostadil is penile pain. The datasheet notes that thirty percent of the patients reported penile pain at least once, This event was associated with only 11% of the administered injections. In the majority of the cases, penile pain was rated mild or moderate in intensity. 3% of patients discontinued treatment because of penile pain. The datasheet for Invicorp[®] describes pain post injection as rare ($\geq 1/10000$ to $< 1/1000$).

General Comments and Study limitations:

- Whilst phase 1 of the VP007 study is a dose finding phase, it showed that significantly fewer patients achieved a grade 3 erection with aviptadil/phentolamine than with alprostadil. Patients were excluded to enter phase 2 if they did not respond to treatment with either aviptadil/phentolamine or alprostadil. Response rates in the second phase of the study may therefore over-estimate those achieved in practice. No statistical comparison of response rates was conducted in phase 2 of the study though response rates were numerically similar.
- Not all patients received aviptadil/phentolamine as the licensed dose and formulation. The proportion of patients who used the licensed dose in phase 2 was not reported. Neither response rates nor safety outcomes for aviptadil / phentolamine 25 micrograms / 2mg, the licensed dose, were reported separately. It is unclear if the doses used in the trial represent clinical practice.
- Reasons for patients drop outs were not specified
- As the trial is open label, patient preference should be interpreted with caution. Notably a low proportion of patients provided patient preference data.

Cost of treatment and Cost Effectiveness:

- Aviptadil 25micrograms/phentolamine 2mg solution for injection (Invicorp[®]) is supplied in boxes of 5 glass ampoules containing 0.35ml solution for injection inclusive of needles.
- 1 box costs £47.50 thus 1 dose for administration £9.50
- Standard comparator therapy is alprostadil injection. Across Hertfordshire, this is most commonly prescribed as Caverject[®] or as its generic preparation (79% ENH CCG, 86% HV CCG). (The remainder is prescribing of the Viridal[®] injection or as its generic preparation). The cost of generic prescribing is equal to brand prescribing. The 10 and 20 micrograms strengths account for the majority of the prescribing.

Caverject [®] Dual Chamber 10mcg	£7.35
Caverject [®] Vials 10mcg	£9.24
Caverject [®] Dual Chamber 20mcg	£9.50
Invicorp[®]	£9.50
Caverject [®] Vials 20mcg	£11.94
Caverject [®] Vials 40mcg	£21.58

- Providing aviptadil 25micrograms/phentolamine 2mg solution for injection (Invicorp[®]) as an alternative to replace alprostadil injection 10 and 20 microgram notes the following cost implications:
 - 10 microgram Caverject[®] preparations (vials and dual chamber): drug cost is likely to increase by £0.26 - £2.15 per syringe
 - 20 microgram Caverject[®] vials: cost reduction by £2.44
 - 20 microgram Caverject[®] dual chamber is of equal cost

Overall with current usage figures, should there be a 100% change from 10 and 20 microgram alprostadil, there is a negligible cost increase

- A cost -analysis is available from both AWMSG and SMC. Whilst both committees' note significant flaws with the cost minimisation analyses submitted, they consider the case for cost-effectiveness is made.
- Whereas aviptadil 25micrograms/phentolamine 2mg is a fixed dose therapy and does not require titration, the comparator therapy does require dose titration. There may be a potential saving from a reduced attendance at titration consultants/specialist nurse visits.

The needs of the population

- The needs of the population appear to be low. Whilst ED is not perceived life-threatening, 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. Alternative treatment options first line and second line are however available and well established.
- Intracavernosal injection therapy is an effective form of pharmacotherapy for ED and has been used for over 20 years. However, because of the invasive nature of the procedure, it is not always accepted to patients and their partners.
- The study population in the VP007 study, the main study for clinical effectiveness data, may not represent the intended patient group. Inclusion criteria were patients with erectile dysfunction for at least one year in a stable heterosexual relationship and over 18 years of age. The intended patient group is for second line treatment, previously treated for ED.
- Comparator intracavernosal treatment with alprostadil can be used at higher doses than the doses used in the study group. Single fixed dose does not allow for dose flexibility.
- A more favourable adverse drug reaction profile including a reduced incidence of penile pain on injection may favour intracavernosal aviptadil/phentolamine. It is therefore possible that this would result in a reduced barrier to this treatment option. However, facial flushing appears to be noted as often observed.
- Aviptadil/phentolamine does not require dose titration. It is therefore likely that this will result in reduced follow up consultant/specialist nurse clinics which may be a favoured option for patient choice. Both SPCs however describe a similar monitoring schedule.
- Has not been studied in men with renal or hepatic impairment.
- SPC advises that no formal studies have been performed in men above 75 years of age.

The needs of the community

- The needs of the community are likely low. Overall drug spend on medication for ED account for a low percentage of the 12 monthly drug spend for ENH CCG and HVCCG. Current prescribing of intracavernosal therapy is limited.
- Overall with current primary care prescribing figures, if there was a 100% change from 10 and 20 microgram alprostadil to Invicorp, there would be a negligible prescribing cost increase
- Drug tariff (May 2019) does not restrict prescribing in line with SLS criteria. The proposed local recommendation is to ensure to prescribe according to SLS criteria. Alprostadil preparations are restricted under the SLS scheme.
- Aviptadil/phentolamine does not require dose titration. It is therefore possible that this will result in reduced follow up consultant/specialist nurse clinics which may reduce financial costs from tariff outpatient appointments. Both SPCs however describe a similar monitoring schedule.

Policy Drivers

- A local Hertfordshire wide primary care prescribing guideline for erectile dysfunction that refers to the use of intracavernosal injections is available for aprostadil cream:
 - Alprostadil cream has a recommendation for restricted use for ED as an alternative option to intracavernosal and intraurethral alprostadil in men who cannot tolerate, have contra-indications to PDE-5 inhibitors or in whom they are ineffective
- Hertfordshire prescribing guidelines for the use of oral phosphodiesterase type 5 (PDE-5) inhibitors for treatment of ED are available
- SMC (November 2017): recommended as an option for use in those who have failed on oral therapies (oral PDE-5 inhibitors) and other non-injectable formulations of erectile dysfunction medications.
- AWMSG (advice no 1117- June 2017): recommended as an option for the symptomatic treatment of ED in adult males due to neurogenic, vasculogenic, psychogenic or mixed aetiology. It is restricted for use in people with ED that have not responded to oral PDE-5 inhibitor therapy
- Local formulary status:
 - Not included in West Essex CCG treatment of erectile dysfunction in primary care guidelines.
 - Not Included in Cambridge and Peterborough CCG Prescribing policy: 'drugs and devices used in the treatment of erectile dysfunction (updated July 2018)' and non-formulary at Cambridge and Peterborough NHS Foundation Trust
 - Not listed in Bedfordshire CCG primary care medicines formulary and not listed as formulary at Luton and Dunstable university Hospital.
 - Included in North Central London Joint Formulary Committee recommendations for erectile dysfunction in men who have failed to respond to oral PDE-5 inhibitors and intracavernosal/urethral alprostadil (approved Nov 2016)

Equity: No impact anticipated. Only licensed for treatment of erectile dysfunction in adult males. There is no impact expected on one or more equality groups differently to others Age; Disability; Gender reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual orientation.

Implementability: No issues identified. If recommended would be AMBER initiation status.

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